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FREUDIAN CONCEPTS OF BRAIN FUNCTION AND BRAIN DISEASE[1]

Their Sources, Scope and Evaluation

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INTRODUCTION

Sigmund Freud's work can be divided into two major provinces, that of the neuropathologist and that of the psychoanalyst. At first approach, these two areas appear to be unrelated and, in a sense, foreign to each other, each of them springing from different sources, using different materials and different methods, aiming at different goals, satisfying different needs and rooted in different biographical situations. But it is *a priori* unlikely that the various chapters of one man's work would deny their author who still remains the same, in spite of the biographical, situational and social changes to which every man's life and thought are subjected. Though we are not the authors of our lives, at least, we are the authors of our books. It is a major purpose of this study to demonstrate the *continuity* of Freud's thought in spite of its apparent disruption.

Freud's neuropathological studies were preceded by neuroanatomical and comparative brain-anatomical ones. From these early studies we learn little about his views on brain function and brain disease. But we must be grateful to his biographer Jones for having stressed in Freud's early studies their phylogenetic and ontogenetic implications thus revealing from the outset Freud's evolutionary thought[3] which proved to be a major constituent of his mature work.

NEUROPATHOLOGY

Turning to his neuropathological studies, we must remember that the term neuropathology was used in Freud's days and in German speaking countries in a sense quite different from the meaning the term finally assumed in our days and particularly in the United States. In Freud's own days and in his own country neuropathology was not understood to be merely a section of pathology, *i.e.* the investigation of altered nervous tissue; its primary purpose was rather to investigate sites and types of brain lesions with the final intention to *correlate* them with disturbed functions and behavior. Thus understood, neuropathology ultimately was intended to open a new avenue to the solution of one of man's oldest, ever lasting and most alarming problems, *i.e.* that of the interrelation of mind and body. Diseases and natural brain lesions can be defined as most daring experiments made by nature herself. The neuropathologist, in

[1] The text of this paper represents a major constituent of a "workshop", given on April 18 and 19, 1958, by the author to the School of Clinical and Applied Psychology, Richmond Professional Institute of the College of William and Mary.

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[3] As shown by Siegfried Bernfeld (2), Freud's evolutionary thought can be traced back to his early teacher Brücke and the Viennese Physiological Institute. Here Freud discovered the way which the spinal ganglion cells have made throughout their evolution; Freud closed the gap between higher and lower animals. The early appearance of Freud's genetic thought was uncovered for the first time by R. Brun (3).

the original meaning of the term, tries to learn from this unique material the laws which preside over the appearances, disappearances and reappearances of functional disorders associated with lesions of different sites and types. The term pathology emerged at a relatively late stage of medical history. Originally it meant no more, but also no less, than doctrine of diseases. Its final and much more restricted meaning was due to increasing specialization, to an ever increasing factual knowledge, to the division of labor, to competence and competition. The neuropathologist Freud remained faithful to the age old tradition; his early studies aimed at a better understanding of man when afflicted by brain lesions and brain diseases. In his most profound neuropathological investigations he studied man at his best, *i.e.* as endowed with speech and comprehension of spoken language. Here are the first links between his beginnings and the years of maturity, when again he studied man at his best, *i.e.* as involved in conflict and relentlessly though not always successfully striving to overcome aggression and hostility.

It was in his monograph on Infantile Cerebral Diplegia (10) that Freud reached, for the first time, a theory of brain function and brain disease which, however, he did neither develop nor formulate in general terms. Contractures of paralyzed members are significant features of the disease to which the monograph was devoted. According to the conventional explanation, the spasticity was attributed to the immaturity, underdevelopment or degeneration of the pyramidal tracts. In contrast, Freud interpreted the symptom in less regional and more general, above all, in more *physiological* terms, as the result of a lack of cerebral influences or stimulations which, under normal conditions, control the activities of lower levels; in positive terms, he interpreted the spastic condition as the result of the activity of an isolated spinal cord, left to itself, since deprived of those influences by which it is reached from higher levels under normal conditions. Lack of myelination, he argued, does not exclude the functioning of the pyramidal tract in the newborn mammal. The correctness of this statement was borne out in our time by a number of studies made by the writer (21–27) on the brains of various mammalian species born with their brains still very immature and not yet myelinated. Similarly, spasticity occurs, Freud added, not only in those instances in which the pyramidal tracts are degenerated, but also in those in which they are congenitally absent. Freud had reached, though only implicitly, the idea of an hierarchical order of central structures or rather functional levels which proved to be one of the most significant elements in Hughlings Jackson's doctrine of nervous function, its evolution and dissolution. There is implied in this view of nervous function the concept of inhibition (of lower levels by higher ones) which Jackson borrowed from Dr. Mercier, a now forgotten but obviously decisive figure in the birth and maturation of Jackson's own ideas, and thereby in the early history of modern neurology. The address in which Jackson acknowledged his debt to Dr. Mercier was published (in BRAIN, 11: 386, 1888), *i.e.*, five years before Freud published his monograph in which he also referred to Jackson. It remains, of course, a matter of speculation whether or not the neurophysiological concepts of inhibition and control may be considered as forerunners of the later concept of repression. A still more daring assumption would be that Freud felt safe in shifting the whole problem from physiology to psychology after he had read the following passage in Jackson's address:

> "I have nothing to say on the nature of the inhibitory process. I would urge, however, that here, as in all other cases, we should distinguish between the psychical and the physical; we cannot legitimately speak of any mental states as inhibitory of any physical processes, any more than we can speak of them as producing movements..." (19).

In the monograph on Infantile Cerebral Hemiplegia, Freud made still other observations difficult to explain by purely regional factors, namely that of the more severe affection of the arm in infantile cerebral hemiplegia and, above all, that of the earlier and more complete recovery of the leg. In a general sense, the phenomenon of recovery always threatens the all-importance of cerebral localization, unless one turns to the activities of spared structures not yet used for the function lost, thereby liquidating indeed one of the fundamentals of cerebral localization, *i.e.* the strict and invariable correlation of a given structure with a corresponding function.

APHASIA

Freud's most significant and conclusive views on brain function and brain disease are to be found in his treatise on aphasia. As I noted on a previous occasion (29), it is one of the most remarkable and distinctive characteristics of the book that it was written by an author, who, as he confessed himself in the very beginning, had no personal observation to offer. This makes the book a rare and brilliant piece of medical thought.[4] Though almost entirely escaping the attention of its contemporaries, it aroused the admiration of more than one informed reader of the next generation. The book carries a vigorous polemic element directed against the then very powerful doctrine of speech centers and one of its most representative apologists, *i.e.* Wernicke.

It is significant that Wernicke's book on the Symptom-complex of aphasia bears the subtitle: a psychological study made on anatomical grounds. In the concluding chapter of his study, the author reminded his readers of the significant criterion of his theory of aphasia which in his own terms rests on the *translation* of anatomical data into psychological ones. Thus was brought home to the reader from the very onset that most unfortunate blending of the two basically different methods of thought which Descartes once strove so hard to distinguish and to isolate. One must conclude that one of the foremost representatives of the first generation which wrote on aphasia in Germany, was decidedly anti-Cartesian. No less significant were the reasons which prompted the author (29) to search for a second speech center, once the existence of the first center discovered by Broca seemed inescapable. Spontaneous or voluntary movements, Wernicke argued, do not instantaneously succeed stimulations; rather do they originate from memory images believed to be revived by external stimulations. In speech we have to deal with sound images the sites of which were shifted by Wernicke to the posterior part of the cerebral hemisphere believed to be sensory in nature. Turning thereafter to results of comparative-anatomical investigations and to the continuity of the third frontal convolution with the first temporal convolution (both being the two branches of the same first "Urwindung"), he focussed his attention on the first temporal convolution as the presumable site of the second speech center. He felt assisted in this assumption by the result of post-mortem examinations, *i.e.* another purely anatomical evidence. Clinical observations appeared only as the last link in this chain of reasonings.

After having drawn an anatomical blueprint of aphasia, Wernicke tried to deduce from his diagrammatic scheme the various types of speech defects resulting from brain lesions. This was the point of departure for Freud's critical study. Freud's opening attack was not directed against the philo-

[4] S. Bernfeld (1) called it "the first 'Freudian' book with all the precious simplicity of style, lucidity of presentation and tantalizing hiding of ideas, as if the reader were as passionate a detective as the writer." E. Stengel's comment (31) reads as follows: "...if any of Freud's pre-psychoanalytical writings could be expected to throw some light on the relationship of the two periods of his working life, and thus on the origin of psycho-analytical concepts, it was the book on aphasia."

sophical implications of Wernicke's basic plan to study, to analyze and to interpret aphasia on the ground of anatomy, but against the usefulness and the actual result of this undertaking when tested by clinical observations. In fact, more than once Freud confessed that he was not philosophically minded. This self-appraisal may sound strange to those who cannot prevent themselves from looking at psychoanalysis as at a contempory version of an age old section of human thought and philosophy, this section still being called by the writers of the eighteenth century moral philosophy. The cornerstone in Freud's doctrine of neurosis is the conflict, *i.e.* an unquestionable moral experience. But Freud's resistance to philosophy was understood to be directed against pre-conceived ideas and speculative systems. It is precisely this resistance and the intrinsically sensualistic or empirical method adopted by Freud which clearly mark his standing in matters philosophical. Here are also the ultimate sources of his opposition to any pre-conceived scheme of aphasia.

Freud selected Wernicke's *conduction aphasia* as a test object. This variety was established by Wernicke himself who attributed its genesis to an interruption of the hypothetical tract connecting the hypothetical auditory speech area with the no less hypothetical motor or speech center, the result of this interruption being paraphasia (mistake in words) in the absence of other symptoms. Freud argued that the interruption ought to result in a loss of repetition of words heard (spontaneous speech and understanding remaining intact); Wernicke indeed believed that speech is acquired by mere imitation and that the ability of reproducing perceived word sounds has been learned *via* the tract believed to be interruped in conduction aphasia. But the faculty of repeating, Freud stated, is never lost as long as speaking and understanding are intact. He concluded that the disturbance of functions attributed to conduction aphasia cannot be deduced from Wernicke's schema.[5] Thus seemed liquidated Wernicke's hope and intention to analyze and to intrepret aphasia in purely anatomical terms; the liquidation was due to reasoning tested by observation. There is embodied in this method the primacy and greatness of human intelligence and the purely instrumental role of observation.

It was not the first time that Freud discussed aphasia. A small chapter on aphasia is to be found in his clinical study on Infantile Cerebral Hemiplegia (12a) which he published with Oscar Rie in 1891, the same year in which his treatise on aphasia appeared. The authors distinguished between speech defects occurring in children who were already in possession of speech prior to the disease and those which affect children as yet speechless. Only the first group was called "true aphasia". Freud was still anatomically minded and he believed this group to be focal in origin, *i.e.*, to result from regional destruction, while he considered the delay in speech development caused by the disease as the result of a more generalized underdevelopment of the brain. Using still stronger anatomical terms, he explained aphasia as the result of a lesion destroying the left speech tract ("die linkseitige Sprachbahn"). Of no less traditional nature was the assumption made in accordance with the teaching of others, that the intact right hemisphere may take over the speech function of the destroyed left one in right-handed individuals or even accomplish it from birth as in left-handed individuals. Unquestionably, there was implied in these statements the belief in regional representations of higher functions or those types of behavior which are known as communication, speech or language. But his genius is palpable in those passages in which he declared aphasia in children suffering from

[5] Conversely, as Goldstein pointed out, the anatomic findings in conduction aphasia, do not correspond to Wernicke's assumption (13, p. 240).

infantile cerebral paralysis, in most instances to be merely a *transitory* and *indirect* symptom, thus giving a wide opening to a less rigid design of cerebral localization. In fact, he admitted remote effects, action at a distance, and he anticipated cerebral shock or diaschisis; the idea of the latter recurred in his paper on aphasia. In his clinical study on infantile cerebral hemiplegia he restricted the scope of the principle of cerebral localization by still another assumption, *i.e.*, that of the *quality* of the lesion likely to produce different symptoms according to its merely irritative or disrupting nature, the *site* of the lesion nevertheless being the same in both instances. It remained undisclosed whether or not at that time Freud was familiar with Jackson's distinction between irritative and destroying lesions. As early as 1870, Jackson had reached the conclusion that nerve tissue may suffer in two ways. "It may be destroyed, and then there is loss of function. It may be unstable, and then there is disorder of function-discharge" (18). He illustrated this distinction by calling forth precisely the same functional disorders which Freud selected in his monograph as test objects for his own distinction between irritative and disrupting lesions, *i.e.*, paralysis and chorea. "In the case of nervous organs representing movements," Jackson said, "we have palsy from destruction and we have irregular movements (chorea) ... from instability." In spite of the surprising identity of views and terms, used by both these eminent authors, we dismiss the rather miserable question of priority or coincidence and we admire the insight gained by Freud into basic problems of cerebral localization at a time when he was still very far from having reached his full stature.

CEREBRAL LOCALIZATION

The demolition of Wernicke's conduction aphasia was not the main target of Freud's polemic. Nor was the criticism of the then popular concept of aphasia the sole intention of his study. He realized that, to quote him, aphasia cannot be treated independently of a broad theory of cerebral activity. Thus, Freud was bound to face the doctrine of cerebral localization; it was indeed under the guise of the latter that the activity of the brain in speech and in general was discussed by his contemporaries. Freud's interpretation of the concept of localization as that of the restriction of nervous functions to anatomically definable areas still stands today as it did almost 70 years ago and Freud's critical evaluation of the doctrine of cerebral localization is as timely in 1958 as it was in 1891. Nor did his argument lose anything of its power and its justification.

We can distinguish several steps in Freud's attempt to refute the theory of cerebral localization. The term "projection" had emerged in Freud's early days as the significant expression of cerebral localization in *anatomical* terms. The term was understood by Freud's teacher, Meynert, to indicate a point by point representation of the body in the cerebral cortex. Freud rejected the assumption of a projection of the body into the cortex in the strict sense, *i.e.*, of an image that is complete and topographically similar. Owing to the *reduction* of the projection fibers on their passages from lower to higher levels, and owing to the *rearrangement* which takes place between the spinal projection and the cerebral cortex, and finally owing to the changing *functional* significance of fibers on their ways through grey masses to the cerebral cortex, the underlying principle, Freud concluded, can only be a purely functional one; the topographic relations are maintained only as long as they fit in with the claims of function. Would Freud have continued this line of thought, he might have reached the principle of "selective inhibition" enunciated many years later by Henry Head. By means of this principle are rejected those afferent im-

pulses which are incompatible with those entering consciousness under given circumstances (impulses of similar quality facilitating each other). In Henry Head's theory of sensation and brain function, inhibition indicates an ultimate stage and final result of the evolutionary process undergone by nervous function. Here was left unnoticed and unused by Freud an early avenue to the principle of *evolution*, which he nevertheless adopted for the interpretation of speech defects in the same treatise on aphasia, and which was to become one of the most significant pillars on which rested his mature thought and psychoanalytic doctrine. But Head's views on sensation did not become known until after Freud had abandoned his brain-pathological studies to engage in an entirely different field.

The second step in Freud's attempt to refute the theory of cerebral localization was made in *physiological* terms. He knew that a *polyglot* affected by a brain lesion, loses a later acquired language rather than the mother tongue. In general terms, the two factors at work in aphasia of polyglots, are the influence of the age of the acquisition and that of practice, both these factors evidently being functional, but not regional ones. At this point Freud cited the famous recurrent utterances, which Hughlings Jackson had observed in aphasics who were practically speechless. One might regard it as very amazing, Freud said, that exactly these cells or these memory traces should have escaped the general destruction. He recalled Jackson's observations in which these utterances were the last words produced before injury and he accepted the Jacksonian interpretation, according to which the persistence of these last modifications of the speech apparatus can be explained by their intensity, if they happen at a moment of great inner excitement, such as it happened to Freud himself according to the following auto-observation:

> "I remember having twice been in danger of my life, and each time the awareness of the danger occurred to me quite suddenly. On both occasions I felt 'This is the end', and while otherwise my inner language proceeds with only indistinct sound images and slight lip movements, in these situations of danger I heard these words as if somebody was shouting them into my ears, and at the same time I saw them as if they were printed on a piece of paper floating in the air ..." (9, p. 62).

It was obvious to Freud that just as the language preserved by the polyglot aphasic, the recurrent utterances resisted explanation in purely anatomical and regional terms. The interpretation offered was a physiological one.

We now turn to Freud's third wave of assault against the theory of cerebral localization. According to the latter, the speech apparatus consists of distinct cortical centers containing the word images (word concepts or word impressions) and linked to each other by the association tracts. Freud objected to a separate localization for ideation and association of ideas. The physiological correlate of an idea, he submitted, starts at a specific point in the cortex and from there spreads over the whole cortex and along certain pathways. We cannot have a preception without immediately associating it, he concluded. His provocative refusal to separate the process of the idea (concept) from that of association, and to localize the two in separate parts, nevertheless proved to have its bearing on a very important section of his whole theory of brain function. It cannot be maintained, he said, that in the so-called centers of speech other, or more important, processes take place than in those parts of the cortical area, the damage of which is better tolerated. The centers obtain their significance only within the framework of pathology but not within that of physiology. At this point, Freud reached the fundamental distinction between localization of *symptoms* and localization of *functions*, this distinction becoming the most significant element in the critical revision to which the doctrine of cerebral localization was subjected by later

writers, above all, Jackson, Monakow and Goldstein.

In more than one passage Freud expressed his disbelief in any localization of the physiological processes underlying speech and he expressed it in various terms:

> "...the speech centres are, in our view, parts of the cortex which may claim a pathological, but no special physiological significance..." (9, p. 67).
>
> "In psychology the simple idea is to us something elementary which we can clearly differentiate from its connection with other ideas. This is why we are tempted to assume that its physiological correlate, *i.e.*, the modification of the nerve cells which originates from the stimulation of the nerve fibers, be also something simple and localizable. Such an inference is, of course, entirely unwarranted." (9, pp. 55–56).

But strangely enough, Freud did not take full advantage of his own conclusion reached by his unprejudiced and critical reasoning. He confessed that "we owe the knowledge of this structure (*i.e.* of the word) to pathology which demonstrates that organic lesions affecting the speech apparatus result in a disintegration of speech..."; thus, once again, we are reminded that pathology could only teach us disintegration; but through the qualifying remark "corresponding to such a constitution" (*i.e.* the word), he conceded that the constitution of speech and words was laid bare by the disintegrating process. Did the qualifying remark not neutralize the first statement that organic lesions result in no more than disintegration of speech?

It seems that at this point Freud could not prevent himself from deriving the *constitution* of language from its *disorders*, or to pass from pathology to physiology. It was left to Henry Head to declare, 35 years later, that the diverse defects of speech do not reveal the elements out of which the use of language is built up; or, in still more unequivocal terms: "The various forms of aphasia . . . show how the use of language can be broken up rather than the elements out of which it is composed" (15, I, p. 477). The reader cannot escape the impression that at this point, Freud did not remain faithful to his own dictum, according to which the speech centers are parts of the cortex which may claim a pathological, but no special physiological significance.

Most revealing is the following sentence: "We have learned to regard the loss of any of these elements (*i.e.* of the word) as the most important pointer to the localization of the damage" (9, p. 73). Originally, he aimed at no more than the localization of the *damage* or the lesion; but still in the second part of his treatise on aphasia, which was no longer critical but intended to offer a constructive solution of the problem of aphasia, he outlined a diagram (9, p. 77) of the word concept in which the old terms of *images* recurred.

Term and concept of *images* or *memory images* were the most significant constituents and criteria of that obsolete version of cerebral localization the destruction of which was the primary aim of Freud's treatise on aphasia. He found it necessary to quote in the opening chapter of his treatise Wernicke's definition of the images in its original terms:

> "The cerebral cortex with its 600 millions of cells, according to Meynert's estimation, offers a sufficiently great number of storage places in which the innumerable sensory impressions provided by the outer world can be stored one by one without interference. The cerebral cortex is populated with such residues of the past stimuli which we propose to call 'memory images'.
>
> "Such images of the speech sounds are supposed to lie enclosed in the cells of the sensory center in the first temporal convolution, while Broca's centre contains the images of the speech movements, the 'glosso-kinaesthetic impressions.' Destruction of the sensory centre causes loss of the sound images resulting in inability to understand language, i.e., sensory aphasia, word deafness. Destruction of the motor centre eliminates the images of the speech movements, thus making the innervation of the cranial motor nerves for the production of speech sounds impossible, i.e. causing motor aphasia. In addition, the motor and the sensory speech centres are linked to each other by a tract of association fibers which Wernicke, in the light of anatomical studies and of clinical observation, located in the region of the insula" (9, pp. 3–4).

In the closing chapters of the same paper,

he outlined his own concept of the organization of the central apparatus of speech; by saying, "... we have refused to localize the psychic elements of the speech process in specified areas ..." (9, p. 67). He nevertheless made use of the concept of images in his final psychological schema of the word concept. Lack of consistency would be the least fault one could impute to Freud. Here were also the sources of his classification of speech disorders resulting from brain lesions.

He conceived the word as a complicated concept built up from various impressions; it corresponds, he stated, to an intricate process of associations entered into by elements of visual, acoustic and kinaesthetic origins.

> "... the word acquires its significance with the 'idea (concept) of the object', at least if we restrict our considerations to nouns. The idea, or concept, of the object is itself another complex of associations composed of the most varied visual, auditory, tactile, kinaesthetic and other impressions" (9, pp. 77–78).

In the light of observations in speech disorders he formed the view that the word concept (the idea of the word) is linked with its sensory part, in particular through its sound impressions, to the object concept. In consequence, he arrived at a division of speech disorders into two classes: (I) verbal aphasia, in which only the associations between the single elements of the word concept are disturbed; and (II) asymbolic aphasia, in which the associations between word concept and object are disturbed. For disturbance in the recognition of objects he proposed the term "agnosia", which has since become technical and irreplaceable. Agnosia may lead to aphasia of the third order or *agnostic aphasia.*

Of all types of aphasia established by Freud, *agnostic aphasia* captures our greatest interest, since it is this type which reflects best of all the significant change to which was subjected the whole problem of aphasia since Freud's early years. Freud did not analyze the dynamics of agnostic aphasia; he merely stated the disabling effect which, in his own terms, disturbances of the visual object associations may have on the speech function and he explained the effect by the special importance that visual object associations assume in certain cases. At this point, he referred to Charcot's teaching, according to whom the preponderance of visual memory images is determined by individual predisposition; they have their local sites in the brain which Charcot conceived as the sum total of isolated organs each of which having a function of its own. It remains an interesting and significant biographical and bibliographical fact that Freud cited Charcot[6] only in a positive

[6] It would be unfair to ignore the passage in which Freud proved to be reluctant to accept all of Charcot's views on aphasia. In fact, Freud's treatise reveals an unmistakable ambivalence of its author towards his great teacher and the views which the latter professed an aphasia:

> "... I believe that the study of the speech disorders has so far provided no reason for attributing any great importance to Charcot's speculations regarding the main aphasic symptoms" (9, p. 99).

A little later, he says:

> "It would certainly be wrong to dismiss Charcot's idea completely and to allow oneself to be misled into a schematic rigidity in the interpretation of the speech disorders" (9, p. 100).

In the preface to his German translation of Charcot's lectures (*Neue Vorlesungen über die Krankheiten des Nervensystems insbesondere über Hysterie.* Leipzig und Wien, Toeplitz and Deuticke, 1886) (7), Freud stressed Charcot's passing from the study of organic diseases of the nervous system to that of the neuroses. The change which took place, due to circumstances, in the interest and teaching of his Paris teacher, strangely recalls the same change which can be traced in Freud's own life and working conditions. One is tempted to conclude that here were sources of identification. The passage in the preface reads as follows:

> "When in the winter of 1885, I came to the Salpêtrière to stay there for almost half a year, I found that Prof. Charcot, then 60 years old, but in full juvenile vigor, had given up the study of organic diseases of the nervous system in order to devote himself exclusively to the investigation of the neuroses and particularly hysteria. This change was associated with the modifications which are described in the opening lecture of this book and which were related

sense; he never attacked the well-known localistic views of his Paris teacher whereas he used all of his polemic vigor against his Viennese teacher Meynert whose views on cerebral localization nevertheless were no more challenging than those of Charcot.

Speech disturbances resulting from visual agnosia were observed by Goldstein and Gelb in their now famous brain-injured patient Schn. These disturbances were summarized by Goldstein in the following words: "the patient's language had lost meaning and showed all the characteristics of the language of an individual who is impaired in abstract attitude." Even if the patient gave correct answers, they represented use of speech instrumentalities without real insight into what the words meant" (14, p. 323). "Language without meaning remains restricted," he concluded, "and is unfit to do justice to the demands of the most essential tasks of the human being. It lacks all spontaneity and creativeness, *i.e.*, the characteristics of man's behavior". We have reached the new approach towards the problem of aphasia. Experienced writers on aphasia, physicians and psychologists are now striving, though under the guise of different terms, for an understanding of speech disturbances resulting from brain lesions, by recalling the basic function of speech in man's existence, his origin and history, individual and social one. But Freud's interpretation of aphasia must be said still to reflect the philosophical and psychological views adopted by his own generation, anxious to fragment man into isolated components and vainly trying to reconstruct him out of these components. We had to learn or rather to relearn that in every analysis, whether neuro- or psychoanalysis of man's behavior, disturbed or not, the full human figure remains the starting point, but not just one of its components.

Thus was finally reestablished a tradition which is linked with the name of W. von Humboldt (17) and his famous investigations on "The Variety of Language and its Influence on the Intellectual Development of Mankind" (1836). There can be no doubt that an inner affinity exists between his work and the major contributions of outstanding contemporary writers on aphasia and that an unbroken line of thought leads from the eminent German philosopher of the early nineteenth century to modern aphasia research.

Language, Humboldt taught, is the organ of *thought*. He asserted that intellect and speech are one and inseparable. The inseparable link of vocal instruments, thought and hearing with speech has its irrevocable and unexplainable origin in human nature, he concluded.

"The difference between languages rests on their forms and these forms are very closely related to the original mental structure of nationalities and to the power pervading them in the moment of their genesis or their renewed meaning.

"Two totally distinct principles come to light while pondering language in general and while analyzing each language: the *sound* and the *use* made of it in order to signify objects and thoughts. This use results from the demands made by thought on speech; hence are developed the general laws of speech; and therefore this part (*i.e.* of speech) is basically identical in all men, excluding the individuality of their intellectual, innate endowments or later developments.... Sound is a part of the whole human organism which stands in close relationship with the inner intellectual power.... The *individual form* of each language originates from these two principles.... They mark the areas, which speech analysis must try to investigate systematically. Here it is indispensable that the undertaking be based on a just and worthy view of language, the depth of its origin and the breadth of its scope...."

"It has been said (6) that Humboldt's essay, which has been called the textbook of the philosophy of speech, first clearly laid down that the character and structure of a language expresses the inner life and knowledge of its speakers, and that languages must differ from one another in the same way and to the same degree as those who

to changing conditions of Charcot's work and teaching in 1882."

It is thought provoking that still another eminent neurologist, C. von Monakow, underwent the same change in his later years. Should we conclude that those who strive for an insight into man and the *dynamics* of his diseases often fail to find in the *mechanics* of the nervous system a life-long and uninterrupted source of interest and knowledge?

use them. Sounds do not become words until a meaning has been put into them, and this meaning embodies the thought of a community. Humboldt finally concluded that "all language, from the simplest, is the fastening of the individual experience to the common nature of man".[7]

Of all formulas ever conceived for a more specific description of this "common nature of man", that of man, defined by E. Cassirer, as an *"animal symbolicum"* (instead of an *animal rationale*) seems to demonstrate the most direct and logical continuity with Humboldt's views; Cassirer considered the symbol to be "a clue to the nature of man". Man, he said, no longer lives in a merely physical universe, but in a symbolic one, implying linguistic forms, artistic images, mythical symbols or religious rites.

From here a direct path leads to Henry Head's definition of aphasia as "disorders of symbolic thought and expression." Head, though historically minded, cited neither Humboldt nor Cassirer whose three volumes on *Philosophy of Symbolic Forms* could have reached him, since their first publication dated back to 1923, a few years before Head's monumental work, *Aphasia and Kindred Disorders of Speech*, appeared. Head understood by symbolic formulation and expression "a mode of behavior, in which some verbal or other symbol plays a part between the initiation and execution of the act." In the disorders of language produced by a unilateral lesion of the brain, "the gravest disorder is shown in the use of such symbols as words and figures. But any form of mental behavior is liable to suffer which demands perfect reproduction and use of any symbol between its initiation and fulfilment" (15, I, p. 210). Head's break with the past and with the views still prevailing among many medical writers of his time and our own, is clearly indicated in the following dictum:

"Acts of symbolic formulation and expression are integrated on a level superior to that of motion, and are of a higher order than sight or hearing. Consequently, the clinical manifestations cannot be classified as 'motor', 'visual' or 'auditory' defects of speech" (15, I, p. 428).

But there is still a second road leading from Humboldt to another great contemporary writer on aphasia, K. Goldstein. In contrast to Head, Goldstein repeatedly cites Humboldt. Cassirer was thoroughly impressed by Humboldt's philosophy of language; he was thoroughly humanistic though experiential at the same time, a shining example of the compatibility of both these perspectives. It is of paramount importance for all those who are willing and able to make heavy demands on their interpretations of speech defects resulting from brain lesions, that Cassirer retained from Humboldt's teaching the result that:

"a language is not simply a mechanical aggregate of terms. Splitting it up into words or terms means disorganizing and disintegrating it. Such a conception is detrimental, if not disastrous, to any study of linguistic phenomena. The words and rules which according to our ordinary notions make up a language, Humboldt asserted, really exist only in the act of connected speech. To treat them as separate entities is 'nothing but a dead product of our bungling scientific analysis'" (4, pp. 120–121).

But above all, Cassirer defined the end of language to be "the ascent to higher levels of abstraction, to more general and comprehensive names and ideas"; he also called it "the ascent to universal concepts and categories". At this point Goldstein's approach toward aphasia and brain injury at large is at hand.

Did Freud succeed in liquidating Wernicke's conduction aphasia? The question can neither be answered by a simple affirmation nor by an unqualified denial. The more recent history of the problem took a new and rather unexpected turn when Goldstein interpreted the picture described by Wernicke as the effect of damaged inner speech, thus calling in a most difficult, much debated and little understood term. He called the symptom complex central

[7] The English translation of the passages quoted was undertaken with the assistance of Dr. G. E. Arrington.

instead of conduction aphasia, "because inner speech seems . . . to be the *central phenomenon of instrumentalities of speech*" (13, p. 94). Goldstein defines inner speech as "*the totality of processes and experiences which occur when we are going to express our thoughts, etc., in external speech and when we perceive heard sounds as language. . . .*"

The following speech performances are tested when inner speech is investigated: the selection of definite word categories by a special language, its syntactical forms and its grammatical structure, the adaptation of the particular speech to the general and special situation in which it takes place, its dependence upon the environment, the listener, etc. The symptom complex of central aphasia resulting from damaged inner speech consists, according to Goldstein, mainly of: (I) impairment of spontaneous speech and understanding, the latter less than the first; (II) literal and verbal paraphasia; (III) paralexia and particularly paragraphia; (IV) disturbance of repetition; (V) disturbance of spelling and of the capacity to combine letters into words. To be noted as not infrequent complications are amnesic aphasia and signs of pure acoustic aphasia (13, p. 231).

In the most recent literature, the concept of central aphasia as a well-defined variety of speech defects resulting from regional destructions in the posterior half of the left hemisphere, is still holding its own, though there are different interpretations of this syndrome. Stengel and Patch (32) interpreted the syndrome as "an incomplete aphasia modified by impairment of the patient's ability to focus attention to word sounds produced by others" (32, p. 415); still, they have "no doubt about the existence of that syndrome, whatever its interpretation" (32, p. 401). Hecaen, Dell and Roger, drawing on interpretations made by Goldstein and by Conrad, but also on observations of their own, trace the syndrome back to a disrupture of a chronological order at the speech level or to a disorganization of the temporal framework: "le cadre temporel se défait . . ." (16). The ability to grasp sequences, but also that to dissect a whole into its sequential parts is lost, and speech thus becomes asyntactic and paraphasic, with repetition impossible.

An element of irony is embodied in the history of conduction or central aphasia. Wernicke's design is not workable, Freud said, since the symptom to be expected after interruption of the tract connecting the auditory speech center with the articulatory one would be failure to repeat words heard (but not paraphasia). In fact, later observers did list lack of repetition among the leading symptoms in conduction aphasia; but by no means did they mean thereby to save Wernicke's anatomical interpretation of speech defects resulting from brain lesions. Freud's criticism still stands, though one of his main targets lost all of its significance; patients suffering from conduction or central aphasia do fail in repetition as indeed they ought to do, according to Freud, should Wernicke's diagrammatic design faithfully reflect the symptoms actually present in conduction aphasia.

THE LIMITATIONS OF FREUDIAN CONCEPTS OF BRAIN FUNCTION

It was seen that Freud interpreted aphasia and all of its varieties in terms solely of interrupted associations.[8] In reading his

[8] Freud's thesis according to which "all aphasias originate in interruption of associations, *i.e.* of "conduction" seemed to gain strong support from two cases, one of them observed by Farges, the other by C. S. Freund, both being listed and analyzed by Freud as samples of "agnostic aphasia" resulting from disturbances in the recognition of objects. In both these cases the speech apparatus proved to be intact, but it failed when stimulated by way of visual object associations only, while it worked correctly when stimulated through tactile object associations. Here, then, observational evidences seemed to lend strong support to the determining role ascribed by Freud to associations and their interruptions in the

aphasia papers, one gains the impression not infrequently that in spite of his anti-localistic attitude, Freud wanted to remain on firm neuroanatomical ground. Neuroanatomy had taught him the existence of tracts and centers as the ultimate components of the central nervous system. After having succeeded in liquidating the centers, he still retained the tracts or associations as the sole constituents of the brain. It thus becomes intelligible that he finally declared all aphasias to originate from interruption of associations. He conceived the organization of the central apparatus of speech[9] as a continuous cortical region, occupying the space between the terminations of the optic and acoustic nerves and of the areas of the cranial and certain peripheral motor nerves in the left hemisphere. When the lesion is situated in the most peripheral areas of this region, and when it puts this center out of action completely, the lesion results in a loss of one of the elements entering into the speech associations. If the lesion is situated in the interior of the so-called speech area, it will, however destructive, cause such reductions of functions, which follow from the general organization of an apparatus of association. Adopting, though slightly misinterpreting Jackson's principles of evolution and dissolution, he believed "that under all circumstances an arrangement of associations which, having been acquired later, belongs to a higher level of functioning, will be lost, while an earlier and simpler one will be preserved..." (9, p. 87). Jackson understood his levels to reflect degrees of complexity, integration and volition of movements; it was a purely physiological scheme, a hierarchy of *functions*; but he never believed the functional levels to reflect chronological ones, *i.e.*, the history of the human race or the human child. Freud's early adoption of the phylogenetic and ontogenetic versions of the principle of evolution, proved to have their lasting effects on his later analysis of human behavior in health and disease. A Darwinian element, entirely foreign to Jackson's view of life and nervous function, found its way into the Freudian concept of brain function, brain disease, aphasia, and finally, into neurosis.

Freud's interpretation of aphasia as the result of interruption of associations undoubtedly was a tribute paid by him to the then powerful associationism.[10] The latter was not unknown to the ancients, but reached its climax for the first time in the philosophical doctrines of Locke and Hume, to be reinstalled in the experimental psychophysiology of Freud's and our own days. It finally became a mighty equipment of the theory of conditioned reflexes. In very general terms, associationism has been said to treat the whole development of the mind as little more than the combination of pre-existing elements (6). In terms of experimental psychology, it is meant to be the formation of functional links between the

genesis of aphasia. However, one wonders whether the observation listed by Farges (the almost speechless patient being unable to recognize her doctor by his voice, but able to do so and to chat with him without any sign of aphasia as soon as he felt her pulse) and that of Freund (the patient being unable to name objects shown to him, but able to do so correctly when allowed to take the object into his hands with his eyes closed)—one wonders whether the difference in result in both tests can be described and explained in Freud's terms of the presence or absence of "respective sensory stimuli", *i.e.* tactile object associations. In fact, it is the test situation *as a whole* with the full impact of *all* stimuli implied and even the *emotional* and more *concrete* implications, past and present ones, which make the difference and which explain the *flexibility* of response in these as in other cases of aphasia.

[9] Stengel recognized the "speech apparatus" as "the elder brother of the psychic apparatus to the working of which most of Freud's later researches were devoted."

[10] As Kris pointed out, the term association assumed in psychoanalysis a new and less mechanistic meaning than it originally had in Herbart's psychology (see M. Dorer, 5). But such is the fate of all concepts. The historian, more interested in the history of ideas than in that of events, discoveries, and men, tries to recapture the original meaning, to test and to interpret the later version in the light of the original concept and thus to differentiate the former from the latter (8, p. 55).

sensations in the course of individual experience (20, p. 652). Associationism suffered its fatal blow from the "Gestalt-theory" according to which all biological and even physical phenomena represent definite structures, *i.e.*, close integral processes, which cannot be decomposed into elements, since each part is fully determined by the whole to which it belongs.

Can aphasia really be explained by interruption of associations? Every experienced interviewer of aphasics makes the observation that the patient may not be able to repeat after the interviewer such simple words as "good-bye", but the same patient, when leaving the room, will say "good-bye" either spontaneously or as a reply. Should we then conclude that associations were interrupted in the first instance, but not in the second one, only a few minutes later? Should we conclude that in the polyglot aphasias, associations are interrupted for a later acquired language but not for the mother tongue? Should we conclude that the recurrent utterances, which an aphasic may produce, time and again, as the sole intelligible speech remnants, are just those in which associations are not interrupted? Aphasics have been observed to retain curses as the only speech remnants. Should we reach the distressing conclusion that the only associations spared are those operating in curses but not in the more noble verbal expressions? Should we conclude that in an aphasic who recovers from his speech defect, the interruption of associations simply ceases to exist and should we disregard his effort and training? Or would it not be more intelligible to explain all these differences in results by differences in *situations*, varying from anonymous and often lifeless test situations to emotionally and socially tinged constellations, taking into account the patient's individual structure, his educational level, his former speech, his anticipations and expectations?

Each theory of aphasia implies a theory of language adopted by its author, willingly or not. Disturbed speech is still speech; it seems impossible to reach an intelligible interpretation of disturbed speech before having reached an intelligible interpretation of speech. Freud obviously did not intend to offer to the readers of his treatise on aphasia a theory of speech. But it is significant that the concluding sentence of the whole treatise reads as follows:

> "...It appears to us, however, that the significance of the factor of localization for aphasia has been overrated, and that we should be well advised once again to concern ourselves with the functional states of speech" (9, p. 105).

Above all, his diagrammatic analysis of the word concept as well as that of the area of the speech associations presuppose the latter as the ultimate roots of speech.

Associations are understood to be the connecting links between preexisting elements, the latter being conceived as images or memory images. The first assumption, that of pre-existing elements, fails to do justice to the new and the creative factor implied in human language, the second assumption, that of memory images, fails to do justice to the very active character of speech as one of man's most significant and noble means of expressing, *i.e.* objectifying his thought by effort, training and intention and by thus communicating with his fellow human beings. Images and their residues spring from outer experience, stimuli and sensations; thus, they are forced upon us, unless we grant the existence of active and integrative powers, operating in the very making of experience and even in the first line of man's conquest intended to reach, to explore and to assimilate the outer world.

On two occasions, Freud could not avoid to hold loss of meaning responsible for the resulting speech disorder. But he did it in terms of images, impulses and associations, thus again, in terms of anatomical and physiological constituents of language, the meaning and significance of which—far from being set by him at the root and origin

of language—was understood by Freud to be the final result of regional cerebral activities.

"... We may assume that the most important source for the association of symbols is the visual area of the cortex, because the visual images usually play the most important part among the object associations. If they are excluded, the speech region can still receive impulses from the remaining cortex, i.e., tactile, gustatory and other associations, and it can still be sufficiently stimulated for speech to be produced. This explains the marked poverty of words of special significance, especially of nouns and adjectives, in patients with asymbolic-verbal aphasia, although spontaneous speech is not abolished even in the most pronounced cases. The words used are spoken mainly on visual stimulation. When stimulated by the other object associations entering the auditory area, the speech region produces a mutilated language, or it transmits all possible stimuli which do not require special object associations, such as particles or senseless syllables (jargon) to the motor pathway serving speech" (9, pp. 84–85).

The brain thus emerged as the ultimate source of man's greatest endowment, *i.e.*, language. Galen would have said, "Man has a brain, because he has language." Freud might have said, "Man has language, because he has a brain." Each of them were in line with the philosophy of their time, Galen being thoroughly Aristotelian, while Freud, at least in his interpretation of speech and aphasia, proved to be an adherent of the brain-materialistic views of his own century.[11] In another crucial passage, he defined words with the most specific meaning as "those which can be elicited by only few and definite associations" (9, p. 89). It was in the same vein that Freud conceived the simultaneous appearance of two aphasic varieties, alexia and symbolic aphasia, as the result of "anatomical contiguity"

"... between the large area of the visual cortex and the cortical field of the acoustic nerve there pass not only the association tracts connecting word and object concepts, but also the tract which serves the understanding of visual letter images. A lesion of a certain localization can therefore, as the result of anatomical contiguity, cause alexia besides asymbolic aphasia" (9, p. 85).

The term "anatomical contiguity" is a very precarious one; it raises but it does neither solve nor relinquish the problem of localization. One has reason to doubt that the neighborhood of structures implies the neighborhood of thought processes; the latter cannot be expressed in terms of structural units, *i.e.*, in terms of space. What may be a great distance in the brain, might be very near in the mind and vice versa. It seems impossible to deny the Cartesian fundamental distinction between *res extensa* and *res cogitans*.

Neither Freud's classification of aphasia nor his interpretation of speech defects resulting from brain lesions has survived. Though his treatise remained practically unknown, and though nobody challenged Freud's views on brain function, brain disease and aphasia, there was little chance for survival in the post-Freudian period which saw the birth and the rise of the Gestalt-theory, which was diametrically opposed to associationism and therefore not likely to adopt Freud's interpretation of aphasia, should the latter ever have reached its readers.

THE IMPACT OF FREUDIAN CONCEPTS OF BRAIN FUNCTION ON PSYCHOANALYSIS

We are able to trace in Freud's own writings the passage from the early and brain-pathological stage of his work to its final and psychopathological one. In 1885 and 1886, when Freud was his pupil, Charcot entrusted him with the task of making a comparative study of organic and hysterical motor paralyses, based upon observations at the Salpêtrière, which might serve to discover some of the common characteristics of neuroses and lead to a conception of their nature. Accidental and personal reasons prevented Freud from following his

[11] We learned from S. Bernfeld that Freud "in his early enthusiasm for the 'physicalistic' physiology swung for a brief period into radical materialism". The period might have been longer then Bernfeld believed.

suggestion for a long time (11, p. 42). Not until 1893 was his paper entitled "Some Points in a Comparative Study of Organic and Hysterical Paralyses" published, in a French periodical.

In this paper Freud referred to his treatise on aphasia (published two years earlier) and the distinction made by him between "projection paralysis" at the spinal level and "representation paralysis" at the cerebral level. He recalled to his readers that the reproduction of the periphery in the cortex is no longer an accurate one, point for point, therefore no longer a true projection. Due to the fact, put forth in his article on aphasia, that fibers coming from the spinal cord to the cortex no longer represent single peripheral elements but rather a group of them; due also to the fact that a peripheral element may correspond to several spino-cortical fibers; due, in brief, to the change in arrangement, cerebral paralysis is no longer a "projection paralysis" but a "representation paralysis". In a sense, he anticipated the contemporary polemic (33) which arose between those neurophysiologists who believe that cortical representation is one of movements, and those who believe that it is one of single muscles. The former view must be traced back to Jackson whose views on evolution Freud adopted. Hysteria, Freud concluded, never simulates the periphero-spinal or projection paralysis; hysterical paralyses show the characteristics of representation paralyses only, though in certain respects important distinctive traits are not lacking between hysterical and cerebral paralyses. In the former, distal segments are not necessarily more affected than the proximal ones and isolated paralyses of individual elements are not foreign to hysterical paralysis; both these criteria, nevertheless, being proper to representation paralyses. Ultimately, the remaining and fundamental difference between cortical and hysterical paralyses was traced back by him to anatomical facts. Every clinical detail of a representation paralysis, he said, finds its explanation in some detail of cerebral anatomy and *vice versa,* we can deduce the structure of the brain from the clinical characteristics of the paralyses. He believed that a perfect parallel exists between these two series of facts. In contrast, he believed, that the lesion in hysterical paralyses must be entirely independent on the anatomy of the nervous system. He concluded that "*hysteria behaves in its paralyses* (showing, as a rule, an *exact delimitation* and an *excessive intensity*) and *other manifestations as if anatomy were non-existent, or as if it had no knowledge of it*" (11, p. 54).[12] But what finally was the nature of hysterical paralysis in positive terms and what was its underlying cause? Adopting the interpretations and conclusions reached by Janet, Freud maintained that it is the common and popular idea of the organs and of the body in general that is at work in hysterical paralyses. The concept of the paralyzed member can no longer enter into association with those other ideas that make up the ego, of which the body of the individual is an important part. In Freud's own and here somewhat cumbersome terms, the lesion would consist in the abolition of the accessibility of the concept of the member in association. Using for the first time the term "subconscious", he concluded, "that the paralysed organ or the abolished function is engaged in a subconscious association endowed with great affective value"; anticipating catharsis, he added, that the paralysed organ becomes free as soon as this affective value is removed. The concluding paragraph of the paper conveyed to the reader his new theory of hysteria which, in the beginning, he still believed to be traumatic in origin. The crucial passage

[12] But does cortical paralysis have a "knowledge" of anatomy, one might ask. In fact, whether or not affected by destroying brain lesions, man has no knowledge of his structures which he throws into action long before he is trained in neuroanatomy. The reader will question the usefulness of man's anatomical knowledge as a criterion of hysterical or organic paralysis.

reads as follows:

> "Every occurrence, every psychic impression is supplied with a certain affective value (Affektbetrag), of which the ego rids himself either by means of a motor reaction or by a process of mental association. If the person cannot or will not free himself of this excess, the memory of the impression acquires the importance of a trauma and becomes the cause of the permanent symptoms of hysteria ..." (11, p. 58).

Associations thus reappeared in the first Freudian design of neurosis; they emerge as connecting links between the neurological and the psychopathological stages of his work. They remained the links between the psychopathological and psychoanalytic stages in which, after liquidation of hypnosis, he turned to free associations as to his final method of unlocking man's secret thought or his unconscious. Thus seems to be established, in a second approach, the continuity of Freud's entire work, in which he never relinquished his ideas of brain function and brain disease.

To investigate and to explain the distinction between cerebral (cortical) paralysis and hysterical paralysis, he had, of course, to adopt at the outset and to reaffirm the conventional and traditional distinction between organic and functional or between somatic and psychogenic. In the early history of nineteenth century psychiatry a long war was waged between the apologists of each of the alternatives, some maintaining the organic, others the psychogenic origin of mental disorders. The distinction between organic and functional or psychogenic remained up to now a significant constituent of our teaching and practice. It has its uncontested didactic and diagnostic value. But it carries a critical element which appears also in Freud's paper on organic and hysterical paralyses.

Charcot had taught him that the lesion in hysterical paralysis is a cortical one, but one of a purely dynamic or functional kind. This qualification, Freud said—amplifying and surpassing Charcot's teaching—is far from being devoid of ambiguity. Though leaving no traces in the nervous tissue after death, he argued, a dynamic lesion (like oedema, anaemia, active hyperaemia) remains a true organic lesion, however insignificant and transitory. He was confident, however, that "the inaccessibility of the concept of the organ or function to the associations of the conscious ego" was a purely functional change, an "alteration in function or mechanism", "without an accompanying organic lesion, at least without a lesion capable of detection even by means of the most delicate methods." Should it then be a matter of time and still greater refinement of methods, one may ask, to reformulate the whole problem and should the alternative organic versus functional no longer remain a fundamental but only a technical one? On the other hand, Freud himself had made precious contributions to the significant role which must be ascribed to psychological factors in organic lesions (*e.g.* the great excitement in which are uttered the last words spoken before aphasia sets in and preserved as the sole remnants of speech). Since then an ever increasing number of observations has been reported by physicians, psychologists and poets, recording and dramatizing the effect of thought and emotion on the manifestations of destroying lesions. These effects are so conspicuous, the answers and the failures of the aphasic so strongly under the influence of psychological factors that Hughlings Jackson isolated a whole area of speech as emotional speech from propositional speech embodying the more conceptual, syntactical and logical constituents of speech.

The Jacksonian definition of the term proposition strangely recalls in its very terms the Aristotelian distinction between utterances, sentences and propositions. A sentence, Aristotle said in his *De Interpretatione*, is a significant portion of speech, some parts of which have an independent meaning, that is to say, as an utterance, though not as the expression of any positive judgment. Every sentence, he also said, has

meaning. Yet every sentence is not a proposition; only such are propositions as have in them either truth or falsity. He selected the prayer as an illustration of this criterion; a prayer, he concluded, is a sentence, but is neither true nor false. Jackson, it is true, shifted this criterion to a more subjective level, by making assent or dissent the criteria of a proposition, but neither objective truth nor falsity. Be this as it may, the reader of the Aristotelian text is reminded of those observations, first reported by Jackson, in which the "speechless man" is still able to swear or to curse, none of these speech remnants having the rank of propositional but only that of emotional speech.

Jackson never cited Aristotle, whose writings nevertheless might have reached him, at least indirectly, from two different sources. Aristotelian influences are unmistakable in Harvey's writings, above all, in his treatise on generation. One is tempted to believe that Jackson, an apologist of evolution, must have been attracted by the same subject, treated by his great countryman morphogenetically, it is true, but nevertheless inspired, guided and strengthened by the Aristotelian concepts of life and growth. I have the feeling of being on still firmer grounds when citing the eighteenth century Edinburgh physician William Cullen as a possible source of Jackson's Aristotelian heritage. Cullen's definition of the nervous system as an organ of animal life and his classification of the manifestations of animal life into motion and sensation, reached Jackson beyond doubt, though in my knowledge he never cited Cullen in his major writings.

At the time when Freud conceived and published his treatise on aphasia and his paper on organic and hysterical paralyses, he confessed to be an adherent of the Jacksonian doctrine of concomitance, according to which a perfect parallel exists between the structural and the functional or the physical and the psychical series. In the light of this theory, the ultimate sources of which are to be found in the writings of Leibniz, and the final destruction of which was undertaken by Henri Bergson, each psychological fact has its physical counterpart; one more reason for Freud, one is tempted to say, to claim rather than to deny a structural basis of "purely" psychological phenomena.

The conclusion seems inescapable that the organic nature of a disease is neither a barrier to its psychologic interpretation nor does the psychologic interpretation preclude for ever organic changes. What may be the ultimate nature or true essence of a natural phenomenon, regardless or independently of our interpretations, remains a matter of pure and transcendental speculation. The interpreter cannot be eliminated from his interpretations and the cognizing mind cannot break through the wall of its own dungeon, nor can it overextend the range of its own instruments; in brief, it cannot cross the borders of human intelligence which looks at the living organism from two angles, the physical and the psychical one, mind and body, leaving it an open question for ever what lies as an objective reality behind these two subjective avenues of approach towards nature. Each natural phenomenon, and disease is one, admits of both these interpretations and no statement on the allegedly organic or psychological nature of diseases, ever outreaches the scope of an interpretation. Thus reduced the alternative organic versus psychological loses much of its significance as a criterion of recognition, though it may still be helpful in reaching practical decisions.

Lasting vestiges of Freud's neurophysiological and neuropathological past can be traced to more than one section of his mature work and psychoanalytic doctrine. He offered intrinsically neurophysiological though genuinely teleological explanations of such basic mechanisms, as pain, conversion, projection, regression and hallucinatory dream (30).

It was in his famous manuscript titled

the "Project" that Freud approached for the first time the problem of pain. Freud started composing the manuscript in a train. It was written in a couple of weeks (in 1895), to be published not until 1950, posthumously. It was intended to offer a theory of the mind in strictly physiological terms. But it also revealed the teleological mode of reasoning, so significant of Freud's mature work, above all, of his interpretation of symptoms as compensatory satisfactions. In his "Project" Freud adopted the principle of inertia as a basic principle of nervous activity. Neurons, he said, have the tendency to discharge amounts of excitations or energies. There exists a true "flight from excitation" ("*Reizflucht*"), those paths of discharge being chosen that put an end to the stimulation. Pain, he concluded, results from (or, as he said, "consists of") an invasion of large amounts of stimuli. In his "Beyond the Pleasure Principle", written about 25 years after the "Project", Freud amplified this theory of pain. He now conceived of a protective shield with which the living substance is provided. He made the assumption that its outermost surface ceases to have the structure proper to living matter, it becomes to some degree inorganic and thenceforward functions as a special envelope or membrane resistant to stimuli. Those were interpretations of greatest scope. Freud probably did not know that the doctrine of the resistant power of the nervous structures was anticipated by Soemmerring (1796); it was outlined in Freud's own days by Jackson and later reaffirmed by this writer (28). Protection against stimuli, Freud maintained, is an almost more important function for the living organism than reception of stimuli. The sense organs, he said, consist essentially of apparatus for the reception of certain specific effects of stimulation; but they also include special arrangements for further protection against excessive amounts of stimulation and for excluding unsuitable kinds of stimuli. The specific unpleasure of physical pain was believed by him to be the result of the protective shield having been broken through in a limited area. How can we expect the mind to react to the invasion of excitations from the part of the periphery concerned to the central apparatus of the mind? His answer was in physiological if not physical terms; *i.e.* in those of charge and energy. The answer reads as follows: "Cathectic energy is summoned from all sides to provide sufficiently high cathexes of energy in the environs of the breach. An "anticathexis" on a grand scale is set up, for whose benefit all the other psychical systems are impoverished, so that the remaining psychical functions are extensively paralyzed or reduced" (12). In less technical terms he described this process of taking up an additional stream of fresh inflowing energy and of converting it into quiescent cathexis, as one of "binding it psychically". He took advantage of these views for the interpretation of traumatic neurosis as the effect produced on the organ of the mind by the breach in the protective shield against stimuli. At this later stage of his work, his thought was no longer psychological but metapsychological; he had returned to brain physiological interpretations.

In conversion, Freud said, the sum total of excitations which cannot enter the associative activities and elaborations enters the wrong path of physical innervation.

To understand the origin of projection, he presupposed the mental apparatus to be shielded against stimuli toward the outside, but not toward the inside. But a particular way is adopted, he argued, of dealing with internal excitations which produce too great an increase of unpleasure; there is a tendency, he concluded, to treat them as though they were acting, not from inside but from the outside so that it may be possible to bring the shield against stimuli into operation as a means of defense against them.

In the hallucinatory dream, the excita-

tion follows a retrogressive course. It communicates itself not to the motor end of the apparatus, but to the sensory end; and finally reaches the system of perception. We call it regression,[13] he concluded, if the idea in the dream is changed back into the visual image from which it once originated.

Trying to grasp and to embrace the psychoanalytic doctrine as a whole, one is impressed by the inner articulation and coherence of the doctrine which emerges as a true system of thought and a well defined body of strongly interrelated interpretations of human nature and human behavior. Rapid readers and expedient listeners frequently use and misuse isolated fragments of this coherent body as easy formulas or panaceas for capturing the never fully disclosed secret of man's existence, past and present. It seems that no doctrine was ever more in danger of becoming handy than psychoanalysis.

It is the inner coherence which the Freudian disease concept has in common with the Greek one (30). The term analysis applies to the same mental procedure in both, with the only difference being that the mental decomposition of the history of disease into its interrelated constituents was shifted from the disturbed bodily functions in Greek medicine to the inner experiences of a disturbed individual in psychoanalysis. The method of thinking, however, remained the same. It is indeed the same mental equipment with which human intelligence tries to approach and to make intelligible the manifestations of diseases at large, physiological and psychological, organic and psychogenic ones. Thus is substituted for the famous mind-body unity, little known and hardly explorable, the unity of man's intellectual equipment which he is bound to use in all of his investigations whether these are aimed at the analysis and understanding of physical or those of psychical phenomena. The unity of Freud's work should be sought in the principles of his investigations rather than in their subjects. Of course, there remains a difference between an aphasic who has lost his speech due to a destroying brain lesion, and a neurotic who fails in communication because he fails in reaching the partner who remains hidden behind the imago of his mother; but by tracing back both conditions to the falling back to early stages of an individual's biography, Freud remained faithful to the same principle of interpretation adopted in his early as well as in his later years. It seems that the inner structure of his thought was finished from the very outset of his career and that it had only to wait for its systematic exposition and elaboration aided by repeated observation and experience.

But we are in danger of ignoring this inner structure, of breaking up the organized whole of the whole system and of storing each of the three basic constituents of the Freudian doctrine, the unconscious, the infantile sexuality and the repression, in nice compartments, to take them out separately and rapidly if needed. Thus originates a well known game for which psychoanalysis is unjustly compelled to furnish the material and the rules. But this is not only degrading; it is above all misinterpreting the doctrine in which each constituent gains its full significance only through its relation to all others. Freud's architectural and occasionally diagrammatical thought might have its share in this now popular application of psychoanalysis to cheap solutions of the complexities and intricacies of human life and disease. We saw that in his early and neuropathological studies, particularly in those on aphasia, Freud did not liberate himself from diagrams and spatial designs of his own. He retained this method of thinking and teaching, and carried it over

[13] Stengel finds in the treatise on aphasia "for the first time in Freud's writings the principle of regression which underlies the genetic propositions of psycho-analysis". It remains true that Freud used the term regression as being synonymous with the Jacksonian term dissolution; the latter, however, has no genetic, *i.e.*, chronological, but only functional implications.

to his mature work; this seems to be another example of the continuity of his thought. In one of his later and more speculative writings, he conceived of the mind "pictorially", looking upon the mind of an individual as an unknown and unconscious id, upon whose surface rests the ego as that part of the id which has been modified by the direct influence of the external world. Making in this passage one of his rare allowances for "popular distinctions" and the non-technical but age old language of man, he added that the ego represents what we call reason and sanity, in contrast to the id which contains the passions. It is revealing and significant that he shifted the passions to the bottom of his diagram or to the depths, or to quote a romantic author to the "darksome side" of man, while he assigned to the ego a surface position. Though he derived comfort and support from the actually superficial position of the cerebral cortex, believed by him the organ of consciousness, it would be unfair to ignore that when discussing the unconscious, he understood his topography of the mind to be a mental, but not an anatomical one.

One might argue that this statement seems to deny the ultimate importance of Freud's early work on brain function and brain disease. But it simply is not possible to cut one section out of a man's life and work and still save the rest.

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PHARMACOLOGICAL REDUCTION OF ABNORMALITY IN MULTIPLE SCLEROSIS WITHIN MINUTES: A STATISTICAL STUDY

RICHARD M. BRICKNER, M.D.[1]

I. PHARMACOLOGICAL REDUCTION OF ABNORMALITY WITHIN MINUTES[2] AS A PHENOMENON PER SE

Prompt reduction (within minutes) of neural deficits of all types in multiple sclerosis, by drugs, has been described by the present author alone and in association with C. R. Franklin, in previous communications (4–10). These findings have been confirmed (2, 3, 17) and some of the techniques modified by others (11, 14).

TECHNIQUE FOR TESTING FOR THE PHENOMENON

In testing for the presence of the phenomenon, the following procedure is employed: One or several symptoms are selected as test objects, and are graded by degree of abnormality as follows: 1, within normal limits; 2, mild abnormality; 3, moderate abnormality; 4, marked abnormality; 5, most marked possible abnormality. It was not difficult to assign scores on this basis. It is useful then to have the patient rest, prone, for 20 minutes, after which the effects of rest upon the selected symptoms may be tested. The drug is then given. The symptom is retested and regraded, clinically or electronically (see below) periodically for an hour, two or three tests being made. The phenomenon is considered demonstrated if unequivocal improvement occurs with a shift upward of at least one grade, and if this effect is duplicable at least once, or is objectively measurable (4–7).

Three of the drugs used (histamine diphosphate[3], amyl nitrite, carbon dioxide) are long-known producers of cerebral vasodilatation; one, Hydergine, is a sympathetic nervous system depressant, with the property of diminishing vasomotor tone of the cerebral blood vessels of experimental animals (11, 13) and of increasing human retinal blood flow (18). Further detail is given below.

The procedures employed (4–10) were not basically meant as a means of therapy; they were intended to be illustrative of the often transient phenomenon of PRA, which is itself of interest.

In studying a given patient, it is essential to learn whether the phenomenon can or cannot be demonstrated at all in relation to one or more specific symptoms, regardless of whether it is transient or permanent in duration. In a word, we are here concerned with the effect itself, and not with therapy[4]. It should be noted that the phenomenon occurs with every type of symptom.

DRUGS, METHODS OF ADMINISTRATION AND RELATED POINTS

The drugs employed in the writer's studies have been amyl nitrite (5 minim ampoules, one to three whiffs); carbon dioxide (5 per cent or 10 per cent with oxygen) given by

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[2] Also referred to as "Phenomenon of PRA" or "PRA". The term "phenomenon of relief by flush" was previously used to designate the phenomenon, in an effort to distinguish it formally from therapy. This term was never satisfactory; the new term, pharmacological reduction of abnormality within minutes, is considered much more accurately descriptive.

[3] In this paper frequently referred to as histamine.

[4] I believe that in my own writing on the subject I may have stressed the therapeutic aspect too much, and have thus distracted attention from the interest possessed by the basic phenomenon itself.

inhalation at the rate of three liters per minute for 5, 10 or 15 minutes; and histamine diphosphate (1 per cent) given by iontophoresis, at 5 milliamperes, until a mild, moderate, or heavy flush (usually at a sub-headache level), as desired, appears. More recently, Hydergine (Sandoz), 0.5 mg. or 5.0 mg. sublingually or 0.3 mg. intramuscularly, has been used.[5] Hydergine was first used in multiple sclerosis by Hirschmann, Bente and Schmid (14), who based their use of it upon the work of Franklin and Brickner (10). Later it was employed by Frick (11) and also by Andreani and Martelli (1).

The hypothesis underlying these studies is that the effects of the drugs are associated with their vasodilating or sympathicolytic, or both, effects.

With drugs producing a visible facial flush, the latter has been used as an indication of pharmacological activity. Obviously, the facial flush is not a measure of the amount of intracranial dilatation, nor even of its occurrence. Intracranial vasodilatation is assumed; sometimes overt evidence for it appears in the form of headache, or a pounding sensation, or gross retinal vein dilatation. We know little of the effects of these drugs on spinal circulation, and have assumed it is similar to that on intracranial circulation.

Early in the present study, nicotinic acid was employed occasionally, but it was omitted later because, at least with the preparations used, it frequently failed unpredictably to produce a visible flush.

The patient remains prone before, during and for at least 20 minutes after the subsidence of the visible flush or for an arbitrary 20 minutes, to help offset sudden hypotension.

In individual cases one drug may be more efficacious than the others in eliciting the phenomenon of PRA. Occasionally, each of two symptoms will respond differently to the same drug and it may require separate drugs to elicit the phenomenon maximally for each. Also, effectiveness of the different drugs may vary somewhat at different times. Obviously, dosage also influences effectiveness.

[5] Hydergine has been kindly supplied by Sandoz Chemical Works, Inc., Hanover, N. J., and histamine diphosphate by Mann Fine Chemicals, Inc., New York, N. Y.

STATISTICAL ANALYSIS

All the material concerning this subject has consisted of clinical observations. To attain greater objectivity in evaluation and interpretation, statistical methods have now been applied. Statistical analyses have been made by an able physicist who is expert in data analysis and who, for personal reasons desires to be anonymous.

The study is of 4458 separate observations made upon 116 patients with clinically unquestionable multiple sclerosis, with a collective total of 311 symptoms (Table 1).[6] For each symptom there was available, among other types of data, the following information: duration of the deficit prior to observation and testing; neurological examination; immediate effect of individual administrations of drugs (*i.e.*, the effect observed in one hour or less); degree of persistence of this effect; and for a number of patients, various types of control data.

RELATIONSHIP BETWEEN RESPONSE AND PRIOR DURATION OF SYMPTOM

The response of a symptom to drugs depends upon its prior duration (denoted

[6] An observation is defined as the observing of the effect of a single drug administration upon a single symptom.

The word symptom is employed, but with some reluctance. There is no other short word which covers the need, but it is possible we are dealing with processes more fundamental than the word "symptom" usually connotes and that the effects discussed here reflect changes in the placques themselves.

In addition to the total of 311 symptoms, there were 35 in which evaluation could not be satisfactorily made: these were excluded from the study.

Most of the recent studies were conducted with ambulant private patients; a few were in wheel chairs.

TABLE 1

Basic Phenomenon of Pharmacological Reduction of Abnormality (PRA) in 1st Hour after Drug Administration

Previous Duration	1 Day or Less		1 Day to 1 Week		1 Week to 1 Month		1 Month to 6 Mos.		6 Mos. to 1 Year		Over 1 Yr.		D Unknown		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	Tallies by Individual Observations															
Phenomenon																
Present	40	100	313	78	421	61	158	40	158	37	194	9	247	62	1531	34
Absent	0	0	87	22	269	39	238	60	267	63	1912	91	154	38	2927	66
Total	40		400		690		396		425		2106		401		4458	
	Tallies by Symptom															
Phenomenon																
Present	16	100	42	86	31	89	28	82	19	73	28	27	41	84	205	66
Absent	0	0	7	14	4	11	6	18	7	27	74	73	8	16	106	35
Total	16		49		35		34		26		102		49		311	

hereafter as D and defined as time between onset of the symptom and first drug administration). In considering the dependence we limit ourselves to answering two questions:

(a) Did or did not this patient, for a given *observation*, exhibit PRA within minutes following administration of the drug?

(b) Did or did not this patient, for a given *symptom*, exhibit PRA?

The answers are tallied (a) with the single observation as the unit (Table 1 and Figure 1) and (b) with the symptom as the unit (Table 1 and Figure 2)[7] but always according to prior duration of the symptom. The number of observations made upon each symptom varied from one to a considerable number so that the total number of individual observations is greater than the total number of symptoms.

The striking dependence of response on prior duration is shown in Figures 1 and 2. Thus, PRA occurred in every one of the 40 observations (Figure 1) made upon symptoms with prior duration of one day or less.

[7] The data for unknown durations and for symptoms of gradual onset are not included in Figs. 2 and 3; there is no appropriate way to do so.

In contrast, with symptoms of more than one year's prior duration, the phenomenon occurred in only 9 per cent of the 2106 observations. There is a gradual decrease in incidence of the phenomenon between these two extremes.

Differences between scoring by observation and by symptom. A higher incidence of positive results is shown when the symptom is the unit of scoring (Figure 2) than when the single observation is the unit (Figure 1). This is because a symptom may show PRA sometimes, although not necessarily in every observation.

For example, a symptom may show the phenomenon definitely in only two out of five observations; that symptom will be scored as showing it; in Figure 2 it will contribute to maintaining at a relatively high level the percentage of positive results. But when the scoring is done according to the percentage of times the phenomenon appeared among all the observations made on that symptom (two out of five in this example), the percentage (Figure 1) will necessarily be recorded as lower.

To employ this point further, the more often the response fails among the observations on a given symptom, the lower

the curve in Figure 1 will be relative to that in Figure 2. A comparison of the two figures shows that the ratio between the two curves (any point in Figure 1 divided by the corresponding point in Figure 2) diminishes continually as prior duration increases; that is to say, *those symptoms which exhibit the phenomenon, do so with less regularity in the longer than in the shorter duration ranges.* For example, the difference between the two curves is slight in the duration range one day to and including one week, but considerable in the next four duration ranges.

The curve in Figure 2 has a plateau in the middle duration ranges; this is due to the fairly constant rate of non-appearance of the phenomenon in these ranges. This contrasts with a 100 per cent incidence of the phenomenon when D is one day or less, and also with a greatly reduced incidence in the longer duration ranges.

Usually, the *completeness* of the response also depends on prior duration; the most complete responses tend to occur with the shortest prior durations, and the least complete with the longest prior durations.

Persistence vs. rapid waning of PRA. The capacity of PRA to last, once it has occurred, is also intimately linked with prior duration of the symptoms involved. PRA can endure for a very long time if prior duration is short enough. When PRA is transient, its average duration appears to be about three to four hours, although this may be briefer, or may extend to several days. This matter will be discussed more fully below.

Confidence Limits. It will be noted that to each point in most of the graphs there is attached a horizontal "flag" which indicates the range of values of D actually associated with this point. For example, in Figure 2, at the second solid point from the left, the flag extends from two days to seven days since in the nominal range—one day to one

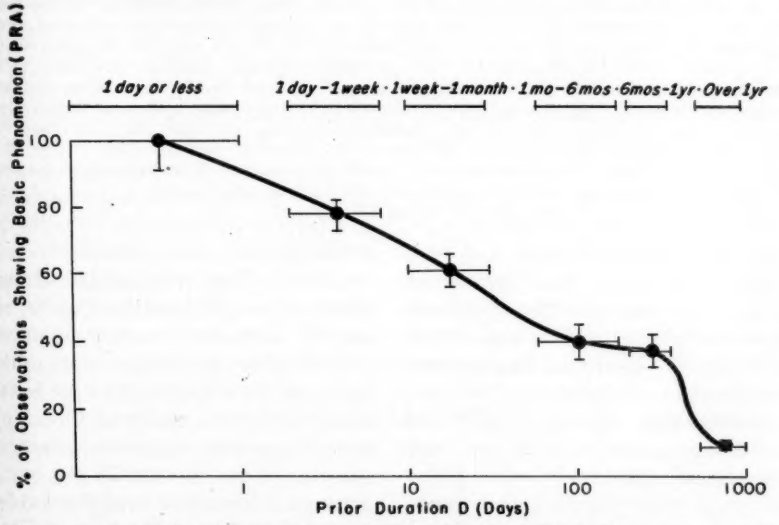

FIG. 1. Incidence of basic phenomenon of PRA tallied by individual observations, divided into groups according to the prior duration (D) of the symptoms upon which the observations are made. The prior durations are: up to and including 1 day; from 1 day up to and including 1 week; from 1 week up to and including 1 month; from 1 month up to and including 6 months; from 6 months up to and including 1 year; greater than 1 year.

The curve shows the percentage of positive observations occurring within each prior duration range.

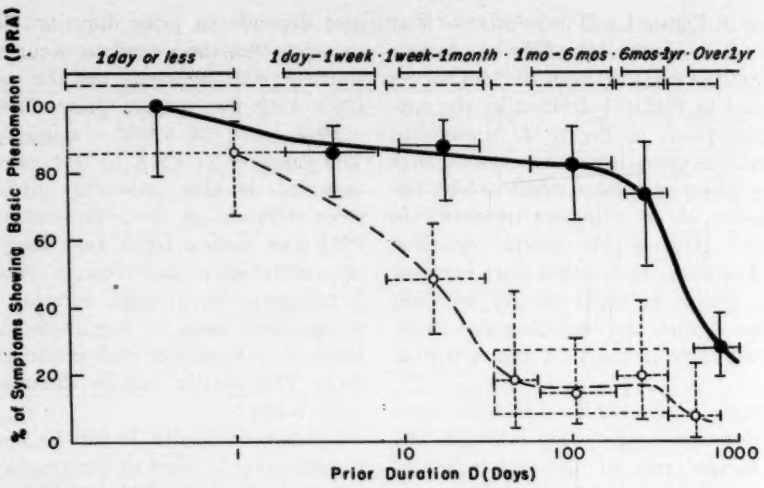

FIG. 2. Incidence of basic phenomenon of PRA tallied by symptoms. The same groups of prior durations of symptoms are used as in Fig. 1.

The curve shows what percentage of symptoms in each prior duration range showed the basic phenomenon of pharmacological reduction of abnormality.

The broken line shows the incidence of spontaneous remissions, for symptoms with similar duration ranges. This curve is drawn from the data of Kurtzke (15). Note that the horizontal flag of the first Kurtzke point extends as far to the right as does the flag of the second R.M.B. point but is obscured by the latter.

As mentioned in the text, Kurtzke has no duration range corresponding to our first one; his first one runs from 0 to 7 days. Also, Kurtzke divided the one-week-to-one-month range into two equal parts and there was a sharp fall-off in the second part. We do not question the actuality of the fall-off somewhere in this region; especially since it conforms with the rest of the Kurtzke curve. However, the two equal parts of this duration range are associated with vertical flags which, in proportion to the corresponding horizontal flags are too long for high statistical confidence. We considered dividing our single duration range into two parts to conform to Kurtzke's, but this produced in our own material, vertical flags which were too long. *In toto*, we deemed it justified to combine Kurtzke's two parts so as to conform to our range, since this made his vertical flags satisfactory.

For explanation of boxed area, see legend for Figure 7.

week—no cases occurred with D under two days. Time is plotted on a logarithmic scale, so that each quarter of the scale represents a multiplication of duration (D) by a factor of 10. The horizontal flags indicate the actual ranges of duration.

The vertical flags associated with each point represent statistical "95 per cent confidence limits" (20).

These limits relate to the obvious question, "How accurate an approximation is the 86 per cent result, which was observed for the 49 symptoms of the above example, to the 'true' percentage, *i.e.*, to the percentage which would have been obtained for an infinitely greater number of instances from which the 49 were presumably picked at random?" This question is amenable to analysis by probability theory; for our specific example the answer may be expressed thus: "If 86 per cent of these 49 instances show PRA and 14 per cent do not, then the chances are 19 to 1 (*i.e.*, one may have '95 per cent confidence') that the 'true' percentage lies between 73 per cent and 94 per cent." Using the available tables of 95 per cent confidence limits, a similar question has been put and answered about each of the points in Figures 1, 2 and 7; the corresponding 95 per cent confidence limits are indicated by the vertical flags.

Other confidence limits may be estimated;

for example, the 80 per cent or 50 per cent confidence limits are roughly two-thirds and one-third as extensive as those indicated in the figure. This broad statement cannot be briefly pinned down more precisely since the exact relative locations of the various confidence limits vary with the specific numbers involved. It should also be noted that the trend of a curve based upon individual points is more to be relied upon than is any one of the points. One may therefore place more confidence in the general trend of the curve in Figures 1, 2 and 7 than in any single one of the points upon which the curve is based.

Comparison with statistics for spontaneous remissions. Statistics representing the incidence of spontaneous remissions have recently been reported by Kurtzke (15); the format he employed is similar to that found essential in conducting the present studies and a comparison is feasible. To be sure, Kurtzke used the whole attack as a unit, and in the present series the most inclusive unit available is the symptom; a curve for the present series, with the attack as a unit would have somewhat longer vertical flags. Another reason for using the symptom as a unit, however, is to avoid losing useful information deriving from differential analysis of the responses of symptoms of different durations. Our symptom-unit, however, seems safely comparable to Kurtzke's attack-unit.

A curve has been drawn from Kurtzke's data, with confidence limits included (insert in Figure 2; also see Figure 7). Comparison of the Kurtzke curve with ours shows that PRA occurs with far greater frequency than spontaneous remissions, except in the second duration range where the difference is slight (Kurtzke has no duration range corresponding to our first one).

Internal consistency of data. The various interrelations between groups of data, as described in the preceding discussion, substantiate the internal consistency of the material.

Predictability of incidence of PRA. From the curves of the first two figures, it is possible to predict with reasonable assurance whether or not PRA may be expected to appear (in unfulminating attacks, especially if the latter are early in the course of the disease; see immediately below).

FAILURES IN THE APPEARANCE OF THE PHENOMENON: WORSENINGS.

Occasionally a symptom fails to show PRA even though new enough to warrant the expectation of PRA, and even though PRA is demonstrable for that same symptom at other times.

Often this results from not selecting the most effective drug or dosage at first; sometimes a more and sometimes a less suddenly and drastically acting drug is needed; in addition, different doses may be needed at different times. Such points must be determined by trial. Occasionally, the failure is thought to be due to an impairment of the patient's general condition; in one instance, a relatively new symptom failed to show the phenomenon until an intercurrent anemia was corrected.

In the presence of a great deal of residual neural damage from earlier attacks, new symptoms are less likely to show the phenomenon than when they occur in relatively intact nervous systems. When a new attack is very fast in attaining its maximal level of damage, especially if a large amount of tissue is involved, it may also block the appearance of PRA. In one fulminating recurrence (D, 5 days) associated with a streptococcal infection of the throat, PRA could be repeatedly demonstrated, but it never endured beyond 10 or 15 minutes. After a few days, the phenomenon itself stopped appearing.

Edema, it is thought, may also block the appearance of PRA. Particularly with initial total failure and later success, it seems quite possible that edema causes the initial failure, and that when the edema subsides, PRA first has a chance to show. Massive

edema does occur in multiple sclerosis; its demonstration, and probably its incidence too, is rare. One patient (seen with Dr. Bela Schick) had an area of localized edema great enough to block the subarachnoid space and necessitate exploration with visualization (Dr. Bronson Ray). The course was otherwise typical of multiple sclerosis.

Occasionally a symptom becomes worse after drug administration, instead of showing PRA; virtually always, this is transient. Rarely, this worsening endures, or a new and lasting symptom appears during the flush; certainly the new symptom, and probably the worsening of the old one, should be deemed a new attack. Schmid has reported some new attacks during the flush (17). These worsenings have not been seen after carbon dioxide or Hydergine administration, but only after use of the more abruptly acting drugs. In the effort to offset the chance of such worsenings, the prone position is employed.

FREQUENT PERSISTENCE OF PRA

A point of particular importance is the frequent long persistence of the relief following a first or other early drug administration, as mentioned above.

Occasionally the symptom disappears entirely after a single drug administration and it does not return throughout a long period of observation (weeks to years). More often, it reaches only a certain level of improvement with the first or other early drug administration; this level, though short of complete abolition of the symptom, still represents a definite and usually marked improvement. The important point is that this level is then maintained. With the next (almost always) drug administration, further improvement usually occurs, following which the symptom often disappearing completely. The level of improvement obtained with this drug administration is also maintained. Thus maintained improvement often occurs in step-like stages.

The only cases included in this "persistence" group are those in which unquestionable improvement appeared within about an hour of the 1st, 2nd, 3rd or 4th drug administration, and persisted. This is important because it marks a sudden, sharply demarcated, lasting change in the state of the symptom involved. The symptom had previously gone on for various periods without change except for minor fluctuations in some cases. No marked or lasting change had occurred in any of the symptoms until a few minutes after one of the first four drug administrations; the change occurring at that time denoted a new event in the course of the symptom.

In almost all cases, the final level of improvement was also attained not later than the 4th drug administration.

Fifty-seven symptoms in 36 patients showed this reduction of abnormality in "pure form." Of these 57, showing the phenomenon after one of the first four drug administrations, 47 showed it after either the first or second. In 24, the symptom was abolished altogether.

Completeness of response, and also speed with which maximum response was reached, are related to the prior duration of the symptom. For example, most of these lasting responses occur when D is not greater than one month; and if D is not over one day, a lasting score of high degree is likely to be achieved on the first drug administration.

Like the incidence of PRA itself, persistance is influenced by the amount of prior neural damage, and the degree of fulmination of the attack under study.

CONTROL OF PSYCHOLOGICAL AND REST FACTORS

Psychological. In considering the results and their implications, the question of possible psychological effects immediately arises. Psychological factors must be deemed existent to some extent in any performance of a conscious human; the important point

is whether their role is minor enough to indicate strongly the operation of other important factors in addition. The probability that they are minor in the present study seems strongly supported by the controlling facts to be enumerated.

1. *Comparison of effect of the drugs upon symptoms of different durations in the same patient.* A group of cases was studied in which, in the same patient, two or more separate symptoms with different prior durations, responded to drug administration with marked differences, as mentioned above. The separate symptoms responded according to their separate prior durations. Nine hundred sixty-seven individual observations of this type were made; the incidence of PRA among them is shown in Figure 3. Comparison of Figures 3 and 1 shows them to be much alike; what discrepancies there are between them are minor, and are explicable by the smaller mass of data represented in Figure 3. Table 2 presents the observations and scores for each duration range.

If there were psychological factors that were determining, they would be attuned to the differing durations of different symptoms in the same patient, and all patients would have to be similarly attuned. These possibilities are, of course, very unlikely.

2. *The frequent persistence of PRA.* This occurrence is regarded as a strong point in controlling the importance of psychological factors and also of spontaneous remissions in interpreting PRA; a result which is, in effect, permanent in this disease (presumably until the next attack), is difficult to explain as psychogenic.

3. *Certain characteristics of PRA.* These have been outlined previously (7). They are the almost uniform timing of appearance of the phenomenon after the drug is given, the repeatability of the phenomenon if the symptom returns in a few hours, and the statistical frequency with which the phenomenon can be demonstrated. The dependence of PRA upon prior duration also indicates that psychological factors are not primary.

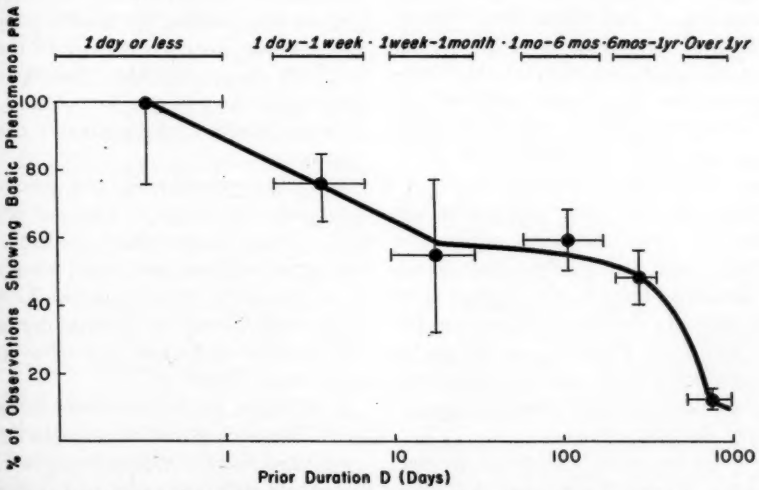

FIG. 3. Incidence of basic phenomenon of PRA among symptoms of different durations *in the same patient* tallied by individual observations.

Observations were made on pharmacological reduction of abnormality in symptoms of different durations in the same patient; and were tallied according to the prior durations of the symptoms. Symptoms of different durations show the phenomenon in relation to prior duration, even when they occur in the same patient.

TABLE 2

Incidence of Phenomenon of Pharmacological Reduction of Abnormality among Symptoms of Different Durations in Same Patient, According to Prior Duration

Tabulation is by individual observations

	1 Day or less	1 Day to 1 Week	1 Week to 1 Month	1 Month to 6 Mos.	6 Mos. to 1 Year	Over 1 Yr.	Total
+	14 100%	55 76%	11 55%	70 59%	97 48%	65 12%	312
0	0	17	9	49	105	475	655
Totals	14	72	20	119	202	540	967

Rest. By common experience, rest may cause transient improvement in neurological symptoms. However, it may not be realized that brief rest may produce sharp, quick changes; these sometimes occurred in the present studies.

Several methods have been used for disentangling from each other the effects of rest and of drug administration.

1. *Relation of the results of control tests and of drug administration to prior duration of the symptom.* For this purpose, the results of mere resting and of drug administration, used on the same symptom in a given patient, are compared.

The number of individual observations of the effect of rest alone is great enough for statistical treatment only if the duration ranges of the symptoms involved are reduced to two: (a) those with D of three months or less, and (b) those with D of more than three months (Figure 4).

The responses after drug administration are related to prior duration, while the changes after rest are nearly independent of prior duration. Thus it is indicated that two fundamentally different phenomena are involved, and that PRA is not simply a rest phenomenon. This method, however, controls the rest factor only with symptoms in the early duration ranges.

2. *The previous night's sleep as a rest control factor in certain instances.* Allusion has been made to instances in which PRA was long-lasting after one or a few drug administrations. Virtually every one of these was, of course, preceded by rest for one or many nights. That period of rest obviously did not produce the enduring improvement which did follow immediately after the drug administration a few hours after waking.

This again bears out the basic difference between rest effects and PRA.

Here, all duration ranges up to one year are controlled, although the preponderance of control is in earlier ranges.

3. *Waning of PRA while the patient is still resting.* More than 50 examples were seen in which the period covering rest and drug administration was sufficiently extended for transient PRA to appear, and then to wane again, though the patient was still resting (*e.g.*, Figure 5). If the effects had been due to rest, they should have persisted until the rest was over. Many of these were in duration ranges greater than three months.

4. *Improvement with rest followed immediately by further improvement with drug.* Often improvement occurred after a rest period without drugs and was sustained at a stationary level for 15 to 20 minutes. This was followed by drug administration, with prompt and marked further improvement (*e.g.*, Figure 5).

5. *Tension of the patient at his first visit.* This is classified here instead of under the psychological heading, because the latter refers to a different order of emotional and mental events.

A patient given a drug at his first or other early visit may be symptomatically at his worst before the first drug administration

because of tension, improving rapidly, independently of the drug, as the tension wanes while he rests. Thus, he might give the observer a false impression of marked improvement due to the drug. This factor was amply controlled by repeated demonstrations of transient PRA, by induction of PRA on symptoms developing after the patient had become accustomed to visits, by noting differing rates of improvement in several symptoms in the same patient and by the steps of improvement over several days when PRA was persistent.

ADDITIONAL CONTROL TESTS

In an effort to gain as much objectivity as possible, and to control the clinical judgment of the examiner, PRA was tested in abdominal reflexes. The recordings were electronically made. PRA was clearly demonstrable by this procedure (12). In addition, a double-blind test is being conducted with Hydergine, the results to be reported separately.

Further, procainization of the stellate ganglion, or of the cervical sympathetic nerve just above it, is under study.[8] Some symptoms from placques presumably in the appropriate intracranial blood bed have shown striking improvement with procainization; this starts as the manifestations of sympathetic paralysis begin to appear, and when it is transient, as in four of the five instances in which it has so far occurred, fading starts, coincidentally with the fading of the sympathetic paralysis. This effect is presumed to be the same phenomenon as that produced by the drugs.

SPONTANEOUS REMISSIONS

All of the demonstrations of PRA occurred within about an hour, and most often within a few minutes. This uniform promptness of effect, as well as the statistical and other controlling factors described above, are considered to render negligible the chance that the occurrence of PRA represents spontaneous remission.

[8] With Leonard Malis, M.D., Ralph Greenberg, M.D. and W. S. Battersby, Ph.D.

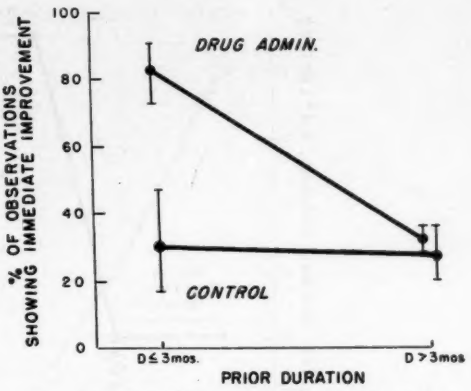

FIG. 4. Curves showing that the effects of drug administration are related to prior duration of the symptom involved, in early duration ranges, while the improvements in the rest-control group are not.

The points are arithmetically accurate; the lines are not meant to imply an algebraic relationship but serve simply to illustrate which pairs of points are associated. Prior duration ranges are condensed.

Control (observations with mere resting). In observations on symptoms with D of 3 months or less, improvement occurred in about 30% (12 out of 40 instances); when D was greater than 3 months, improvement occurred in about 27% (37 out of 135 instances).

Observations with drug administration in the same group of patients. Observations on symptoms with D of 3 months or less showed improvement in 83% (76 out of 92 instances); when D was greater than three months improvement occurred in 32% (217 out of 681 instances).

The drug responses are closely related to prior duration of the symptom, in early duration ranges, while the improvement due to rest are only slightly related if at all.

In discussing the evaluation of therapeutic attempts in multiple sclerosis, and its difficulties, McAlpine, Compston and Lumsden (16, p. 204) say, "The difficulty here again is the extreme variability in the duration of relapses. Brickner (1952), in discussing the evaluation of vasodilating drugs in the treatment of acute episodes, suggests the effect of the drug should be immediate and that there should be a predictable repetition in its effect. With other

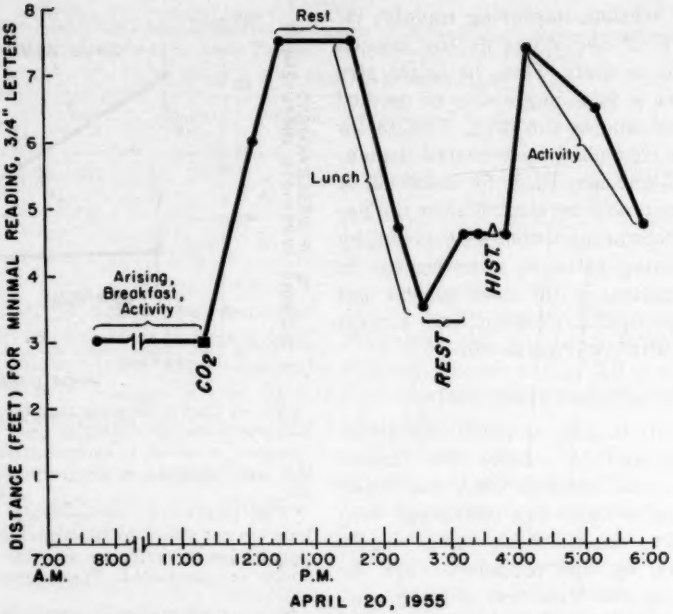

FIG. 5. Effects of rest and activity on visual acuity and demonstration of PRA

Rapid transient improvement in visual acuity (O.S.) associated with drug administration, twice in one day. The day's gross events are indicated.

Note especially the amount of improvement associated with rest just before the second drug administration, and how much greater is the improvement with the drug. This is the major matter demonstrated by this figure at this point. The effects of activity are also to be noted.

remedies that may be used in the future a rapid rather than an 'immediate' response might suffice. For example, if a series of a dozen or more cases of acute retrobulbar neuritis had shown no visual or perimetric improvement at the end of a week, then responded within twenty-four to forty-eight hours to the same form of treatment, and in a control series the rate of improvement was considerably slower, such a result would be significant. The same criteria could be used for an acute relapse characterized by sensory symptoms."

My belief is that the essentials of these requirements are exactly what have been met. This is especially well shown by the 57 examples of pharmacological reduction of abnormality in "pure" form. One of these is represented by the graph in Figure 6. The patient had had complete astereognosis of the right hand, of ten days duration; improvement which had not occurred before, began coincidentally with the first drug administration, and was completed in two steps, the symptom disappearing entirely, and not returning according to follow-up reports covering eight months.

I differ with McAlpine *et al* somewhat in regard to the particular type of control series they suggest at this point. A group of unmedicated patients would be only partly an adequate control for the "immediate" type of observations described here (actually, it is available in our own rest-control group and also in Kurtzke's series). The incidence of the phenomenon must be controlled in other pertinent ways as well, and I believe that it has been with respect to psychological controls, dependence on prior duration and other factors

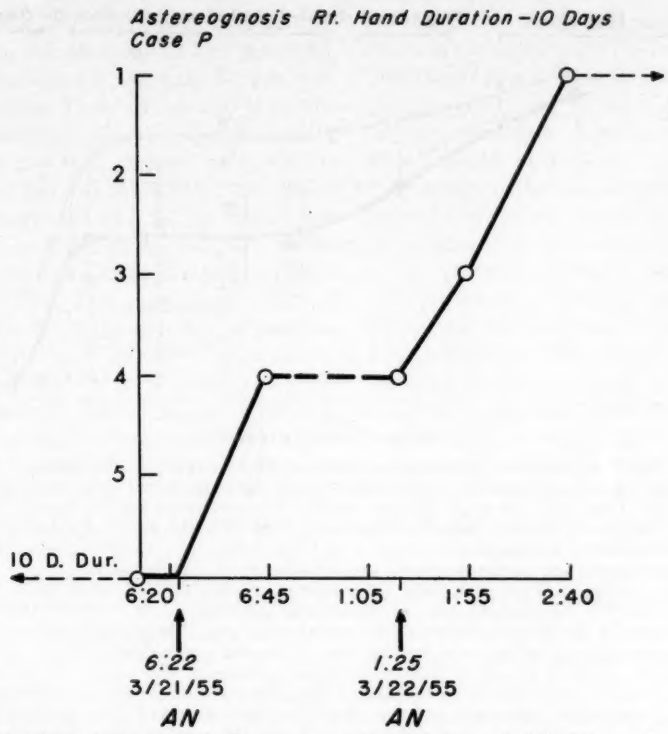

FIG. 6. Abrupt improvement of a symptom with first drug administration, after ten day history.

An instance of lost position sense in the right hand, stationary since the onset 10 days previously according to the history given by the patient; immediate moderate improvement after a single administration of amyl nitrite, lasting until a second administration of amyl nitrite the next day. With the second administration, immediate further improvement, to normal. The condition remained normal for as long as the patient was followed up; about eight months.

The history period, and the overnight period between the last test on 3/21 and the first on 3/22, are indicated by broken lines because no tests were made by us during that period. It was necessary to accept the word of the patient, who made her own tests, that there had been no recession.

previously discussed. In addition, it seems to me somewhat safer to focus on an "immediate," rather than a "rapid," response.

II. EMPLOYMENT OF THE PHENOMENON FOR THERAPY

PRA does often lend itself to therapeutic usefulness. The 57 "pure form" occurrences of the phenomenon discussed above, were, of course, therapeutically useful. But many more cases in addition showed a therapeutic effect.

Many occurred after a larger number of drug administrations than four (this was the upper limit of the "pure" group). In many, plateaus of therapeutic effect were interspersed with considerable fluctuation, another fact excluding them from the "pure" group. But every plateau did start with a given drug administration, and in every case a sustained plateau was ultimately reached, again in associtaion with a given drug administration.

Figure 7 presents the proportion of times,

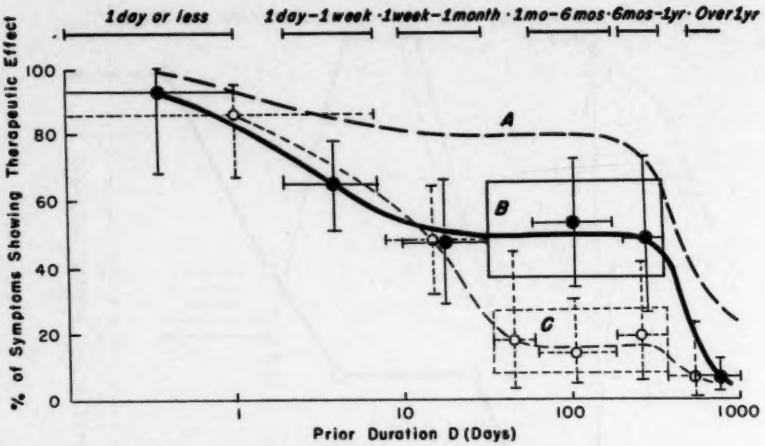

FIG. 7. Incidence of therapeutic utility of PRA (tallied by symptom)

Line A is Fig. 2 of the present paper, added to this figure in dotted lines, to make comparison easier (flags and one guide line are omitted to avoid confusing the figure). Line B shows the therapeutic results, tallied by symptom. Line C is the curve of Kurtzke's data again introduced for comparison.

Prior durations ranges of the symptoms are the same as in Figs. 1 and 2.

The curve shows in what percentage of symptoms in each prior duration range it was possible to employ the phenomenon for therapeutic purposes.

As described in the text, Kurtzke's second and third duration ranges were combined into one (shown here as his second one) for the sake of sounder comparison.

In order to obtain a greater degree of statistical confidence, and to reduce the size of the vertical flags, the one-month-up-to-and-including-one-year prior durations were grouped together, in both Kurtzke's series and our own. The boxes show the extents of horizontal and vertical flags pertaining to that grouping; note that the vertical flags of the two series do not overlap. (Even without making this combined grouping, the degree of overlap in these ranges is small.)

according to duration of symptom, in which PRA could be turned to therapeutic value.

The comments concerning the nature of Figures 1 and 2 are applicable to Figure 7. The curves have a similar shape, as would be expected, for they originate in common anatomical, physiological and pathological factors.

The therapeutic effect, like the basic phenomenon, is dependent on prior duration of sympton. Comparison of the incidence of therapeutic effects with Kurtzke's statistics for spontaneous remissions (Figure 2 and Figure 7, B and C), shows the greatest therapeutic effect in the duration ranges of one month to one year inclusive. In fact, there is no statistical difference between the two series in the first three duration ranges and in the final one.

Despite this lack of statistical difference in the shorter duration ranges, the chance of a therapeutic response probably approaches unity in those very ranges because the drug-induced improvement can be brought about almost at will. This must mean that at the moment the drug is used, there is a potential for reversibility of the symptom which is not being realized spontaneously. Thus the drugs add a factor of safety in those early duration ranges; first, the improvement is brought about in a controlled way, and secondly, the more prompt the remission, the less is the probable residual permanent damage. In future attacks, new symptoms will probably remit more readily if on a background of relatively little earlier damage.

In the D range, one month to one year inclusive, the potential for reversibility of damage is realized spontaneously in only

16 per cent of the instances; the drug procedure aids the fruition of this potential, giving a therapeutic result in 51 per cent of the instances. Thus, a symptom of middle duration range can often be made to behave like a younger one, through this realization of potential. Likewise, there is a ceiling on this employment of PRA for therapeutic fulfillment, exceeded in its own turn by the mere transitory occurrence of the phenomenon (Curve A). This may mean that still more fulfillment of the potential is possible, but that only part of such excess can be made to endure. In other words, the difference between Curves A and C is considered a measure of the existence of reversibility factors; the difference between B and C a measure of the capacity of these factors to dominate the course of the lesion, and the difference between A and B of the relative tenuousness of the factors.

The virtual identity of the early parts of the curves for Kurtzke's and our data constitutes a mutual confirmation of accuracy.

Predictability of therapeutic result. From the curves of Figure 7, it is possible to predict with reasonable assurance whether or not a therapeutic result will occur, in unfulminating attacks, especially if the latter are early in the course of the disease.

Lack of prophylactic value. Obviously, the procedure does not lend itself to prophylactic use against future attacks.

Controls. The same control factors which were used for PRA itself apply also to therapy, in excluding psychological and rest effects and spontaneous remissions. It may be especially re-emphasized that, according to the specific type of procedure employed here, a therapeutic effect to be deemed real, must be a direct, uninterrupted continuation of the phenomenon itself, time limits included. One should ask the question, "Did the continuing improvement commence within minutes or at most an hour of one of the administrations of the drug?"

Value of distinguishing between the basic phenomenon and its therapeutic application. A certain persistent error has occurred in the minds of many neurologists; it also exists in the literature. It is failure to recognize the drastic difference between PRA on the one hand, and its therapeutic application on the other. Instead, the two have been thought of as one.

This fundamental misidentification has led to other misunderstanding. Hence many physicians have given the drugs for therapeutic purposes without checking the immediate result, and by necessity have thus overlooked the incidence or absence of PRA itself. Patients have been routinely instructed to take a drug at some routine frequency, reporting back at a stated interval such as a week, for evaluation. Thus gross evaluation of a whole group of patients is substituted for well-timed individual observation of symptoms within an hour of drug administration, the whole point has been missed and the opportunity has been lost to test out therapeutic possibilities on the basis of the patient's immediate symptomatic reaction to the drug. The spontaneous remission factor cannot be controlled in this way, nor can there be any of the interesting and fruitful experience which the unerring employment of the procedure can give.

SUMMARY

1. A statistical study is reported of the phenomenon of pharmacological reduction of abnormality within minutes (PRA) in multiple sclerosis (this was previously termed "relief by flush"). This phenomenon is the reduction within an hour or (usually) less, of neural deficits in multiple sclerosis, after the administration of certain drugs.

2. It is the phenomenon itself which is of major interest, and not its therapeutic application. In studying a patient, the essential thing is to learn whether the phenomenon can or cannot be demonstrated in relation to one or more specific symptoms, regardless of whether it is transient or permanent in duration, and regardless of any possible therapeutic utility.

3. Neural deficits of every type are equally affected.

4. The drugs chiefly employed have been histamine diphosphate, carbon dioxide and amyl nitrite, which have in common the production of intracranial vasodilatation, and Hydergine (Sandoz).

5. The study is of 4458 separate observations, on 311 symptoms in 116 patients.

6. The producibility of PRA and the length of time it lasts are largely dependent on the prior duration of the symptoms involved. With symptoms of brief prior duration, PRA is much more likely to occur with predictable regularity, to be marked and to be enduring, than with symptoms of long prior duration. Extensive neural damage residual from earlier attacks reduces the chances of occurrence of the phenomenon.

7. The incidence of PRA is far greater than that of spontaneous remissions, according to a comparison with the data of Kurtzke concerning spontaneous remissions.

8. The phenomenon is not dependent on spontaneous remissions, psychological factors, nor rest, as attested by control data.

9. The phenomenon often lends itself to therapeutic uses. The same control methods used for the phenomenon itself in excluding psychological, rest and spontaneous remission factors, are employable here.

10. In many cases a lasting effect follows a single drug administration. This is regarded as a demonstration of the phenomenon, and of its therapeutic applicability in "pure form." It means that the indicated symptoms ran an unchanged course from their onset until a few minutes after the first or other early drug administration, at which time a lasting change occurred.

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A PSYCHOPHARMACOLOGICAL TEST OF THE "BODY IMAGE" HYPOTHESIS[1]

ARTHUR B. SILVERSTEIN, PH.D AND GERALD D. KLEE, M.D.[2]

The basic hypothesis underlying the interpretation of human figure drawings is that the figures represent the subject's body image, defined by Schilder (11) as "the picture of our body which we form in our mind." In a recent review of research on figure drawings, Swensen (15) found few studies pertinent to the "body image" hypothesis, and he concluded that "there is slight basis for believing that the figure drawn usually represents the subject's own body." Among the investigations cited in this review, there is not one in which the investigator sought to produce body image changes in his subjects experimentally, and then determine whether these changes were reflected in their figure drawings. There are a number of ways in which such a study might be carried out. The use of hypnosis to induce alterations in sensory or motor functioning, presumably accompanied by changes in body image, is an approach that might prove fruitful. Another possibility, represented by the study reported here, is a psychopharmacological test of the "body image" hypothesis.

Body image changes are among the most dramatic symptoms produced by lysergic acid diethylamide (LSD-25). Virtually every investigator since Stoll (14) has remarked on the striking effects of the drug on body image. Savage (9) has given a particularly graphic and detailed account of the progression of these effects, from the pathological accentuation of body image shortly after the ingestion of LSD-25, through the manifold distortions that are experienced somewhat later, to the eventual loss of the boundaries of the body image, accompanied by estrangement and depersonalization. Such symptoms as these suggested the use of LSD-25 in an experimental test of the "body image" hypothesis. Paintings and drawings illustrating the drug experience have appeared in a number of papers (2, 6, 7, 8, 10, 16), but the literature contains no systematic comparison of figures drawn under the influence of LSD-25 with those drawn by the same subjects under control conditions. The present paper reports the results of such a comparison.

[1] The study reported in this paper was conducted under the guidance and supervision of Dr. Jacob E. Finesinger, Director of the Psychiatric Institute.

[2] The Psychiatric Institute, University of Maryland School of Medicine, Baltimore.

PROCEDURE

The subjects were 18 male college graduates between the ages of 20 and 24, each of whom had had a physical examination and a psychiatric screening interview prior to the start of the study. Figure drawings were obtained from the subjects under control conditions, and also after they had ingested 72 mcg. of LSD-25 in distilled water. The conventional procedure was followed: the subjects were first asked to draw a person—a whole person, and then a person of the opposite sex from the first. Finally, they were asked to draw a picture of themselves. No time limits were set, and no further directions were supplied. Half the subjects in the sample made their drawings first under control conditions, and again two days later, at approximately the height of their reaction to the drug. For the other half of the sample, the order of the two conditions was reversed.

STUDY OF JUDGMENTS

The drawings of the male, female, and self figures were treated separately. The figures drawn by each subject under control and drug conditions were paired in random order

and then given to four judges, with instructions to identify the figure in each pair that had been drawn under the influence of LSD-25. Two of the judges were clinical psychologists, trained and experienced in the psychodiagnostic use of figure drawings, but with no first-hand knowledge of the effects of the drug. The other two judges were psychiatrists who had worked for some time with the drug, but who had had no formal training or experience in the interpretation of figure drawings. For the benefit of the psychologists, LSD-25 was described as "a drug that produces symptoms resembling those of schizophrenia in some respects, and those of the toxic psychoses in others." They were also told some of the common effects of LSD-25 on body image, as reported by subjects in the drug state. All the judges were told the general characteristics of the sample: age, sex, and educational level, but the individual drawinge were identified by name only.

RESULTS

The first step in analyzing the data was to determine the reliability of the judgments. Table 1 presents a summary of the numbers of agreements between the six possible pairs of judges. The significance of the results was evaluated by means of the binomial distribution, which was also employed in most of the tests of significance to be reported below. Judgments of the female figures tended to be more reliable than those of the others, three of the judges obtaining perfect agreement in identifying the female drug figures. The reason for this difference is not apparent. The data gave no indication of a higher level of agreement between judges in the same profession than between judges in different professions.

TABLE 1

Reliability of Judgments of Human Figures Drawn under Control and Drug Conditions

	Male	Female	Self
Median	13*	17**	14*
Range	11–16**	16**–18**	11–15**

* Significant at .05 level.
** Significant at .01 level.

The validity or accuracy of the judgments was then determined. Table 2 shows the numbers of drug figures correctly identified by each judge. These data were subjected to Friedman's two-way analysis of variance (13), which revealed that the three figures did not differ significantly in the accuracy with which they were judged, and that the four judges also did not differ significantly in their ability to identify the drug figures. On the other hand, as all the judges indicated after they had made their identifications, the individual subjects varied greatly in the ease with which their drug and control figures could be differentiated. Five of the 18 subjects had every one of their drug figures correctly identified by all four judges. In contrast, there was one subject none of whose drug figures was correctly identified by any of the judges. The male figures drawn by this subject under control and drug conditions appear in Figure 1. It seems clear that the quality of his drawing actually improved under the influence of LSD-25, and the same was true for his female and self figures. There was nothing in this subject's psychiatric interview material that would appear to account for his improved performance in the drug state.

When the judges had completed their task, they were asked what cues they had used or had attempted to use in arriving at their judgments. As might be expected from the relatively high reliability of their judgments, there was considerable consensus in the cues that they reported. Cues most often mentioned for identifying the figures drawn under the influence of LSD-25 can be grouped as follows: larger size, more disturbed line quality, less attention to detail, and a greater number and severity of distortions. Each of these cues was cited by at least three of the four judges.

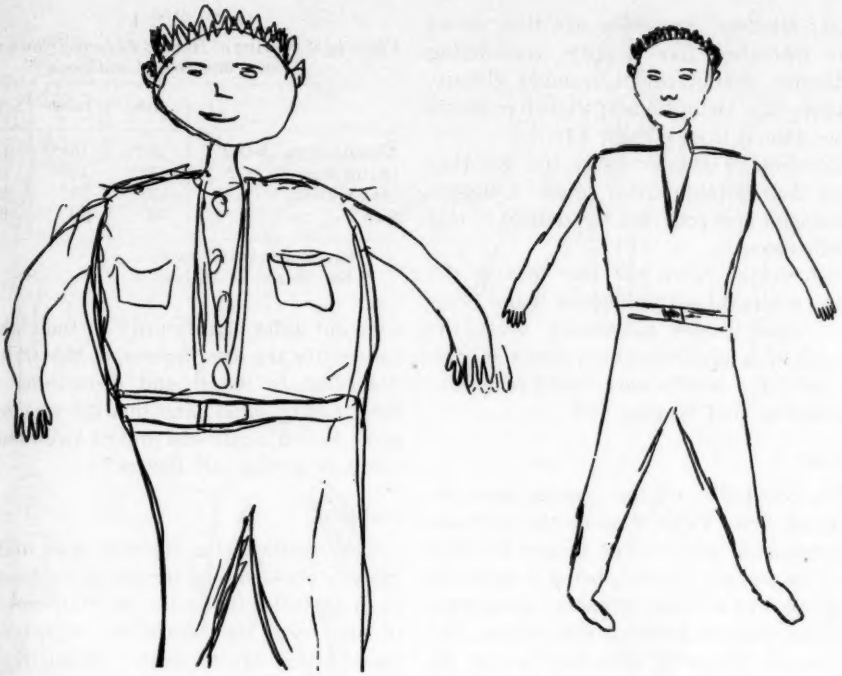

FIG. 1. Male figures drawn under control (left) and drug (right) conditions

COMMENT

The results of the study of judgments indicate that the judges were able to differentiate, both reliably and accurately, figures drawn under the influence of LSD-25 from those drawn under control conditions. However, the purpose of this investigation was not to develop a method of bio-assay for the drug, but to test the "body image" hypothesis. That the judges could identify the drug figures is thus not as pertinent as that the cues they reported using are consistent with what is known about the body image changes produced by LSD-25, from sources other than figure drawings. Nevertheless, an independent empirical test of the validity of these cues was considered desirable, to determine whether they were in fact the ones that had enabled the judges to identify the drug figures as well as they had, and to establish their relative value in differentiating drug from control figures.

TABLE 2

Validity of Judgments of Human Figures Drawn under Control and Drug Conditions

Judge	Male	Female	Self
Psychologist K	15**	15**	16**
Psychiatrist P	12	15**	15**
Psychologist I	14*	15**	12
Psychiatrist D	11	15**	11

* Significant at .05 level.
** Significant at .01 level.

STUDY OF CUES

The drawings were presented to two additional judges, both clinical psychologists, with instructions to compare the figures in each pair with respect to the four cues mentioned in the study of judgments. For each of these cues, specifications were drawn up with the aim of increasing the objectivity of the scoring. An abbreviated version of these specifications follows:

Size: Score the larger figure in each pair.

Line Quality: Score the one that shows more disturbed line quality, considering continuity, reinforcement, tremble, closure, and pressure. Definitions of these five points were adapted from Caligor (3).

Attention to Detail: Score the one that shows less attention to detail. Caligor's monograph also provided the details of this specification.

Distortions: Score the one that is the poorer portrayal of the human figure. This specification seems to convey what the judges had in mind when they spoke of "distortions." Its details were based primarily on Schubert and Wagner (12).

RESULTS

The reliability of the scoring was determined first. Table 3 gives the numbers of agreements between the judges for each cue. The scoring for size, being completely objective, was perfectly reliable—there were no disagreements between the judges. The scoring for the other cues was not as reliable as we had hoped to make it in drawing up the scoring specifications, but it was nonetheless regarded as satisfactory.

The judges resolved their scoring disagreements in conference, and the validity or accuracy of the resolved scoring was then determined. Table 4 shows the numbers of drug figures correctly scored on the basis of each cue. These data were subjected to Friedman's two-way analysis of variance, which revealed that the three figures did not differ significantly in the accuracy with which they were scored, but that the four cues did differ significantly in their ability to identify the drug figures, at the .05 level. Attention to detail and distortions were both highly valid, line quality was somewhat less so, while size proved valid only in the case of the self figures.[3]

TABLE 3

Reliability of Scoring of Human Figures Drawn under Control and Drug Conditions

Cue	Male	Female	Self
Size	18**	18**	18**
Distortions	16**	16**	14*
Attention to Detail	15**	13*	16**
Line Quality	16**	13*	15**

* Significant at .05 level.
** Significant at .01 level.

TABLE 4

Validity of Scoring of Human Figures Drawn under Control and Drug Conditions

Cue	Male	Female	Self
Attention to Detail	16**	16**	15**
Distortions	15**	15**	16**
Line Quality	13*	13*	15**
Size	10	10	14*

* Significant at .05 level.
** Significant at .01 level.

COMMENT

The results of the study of cues indicate that the cues cited by the judges in the study of judgments (with the partial exception of size), were, in themselves, valid for differentiating figures drawn under the influence of LSD-25 from those drawn under control conditions.

DISCUSSION

To point up the consistency of the findings of this study with the "body image" hypothesis, a portion of Savage's account of the effects of LSD-25 on body image (9) is presented here. The points that he makes in his description of the height of the reaction to the drug are illustrated by some of the drawings obtained in the present study:

"With this phase many changes can be observed in body ego feeling. The unity of the body cannot be maintained; the parts of the body seem dislocated. Limbs feel detached and floating. (Figure 2,A) The symmetry of the body is lost, and it assumes enormous plasticity. It becomes warped and

[3] A recent study (5) found a significant increase in the size of the figures drawn by schizophrenic patients under the influence of LSD-25; the figures drawn by normal subjects also increased in size in the drug state, but the difference was not significant. Self figures were not obtained in this study.

FIG. 2. Human figures drawn under control (left) and drug (right) conditions. A. Female figures. B. Self figures. C. Male figures. D. Female figures. E. Self Figures. F. Male Figures.

distorted in every direction.... (Figure 2,B) The body may feel large and inflated, (Figure 2,C) or so small that the individual fears lest he be stepped on....[4] (Figure 2,D) The body may become separated from the individual so that he feels himself sitting

[4] Only a few subjects drew drug figures appreciably smaller than their control figures.

off in a corner or standing in back or [at] the side of himself.... (Figure 2,E) With the changes in body ego feeling are associated changes in the ego boundaries of the body. Ego feeling is withdrawn from them, and they become weakened, fluid and variable. It becomes increasingly difficult to tell where the body leaves off and the rest of the world begins. (Figure 2,F)"

Considering the four cues in order of decreasing validity, we regard the decreased attention to detail in the drug figures as a sign of the primitivization, or regressive dedifferentiation of body image produced by LSD-25. The increase in the number and severity of distortions seems to reflect the fluidity of body image in the drug state—changes in shape, disproportions, asymmetry, etc. The more disturbed line quality we would relate to changes in the body-image boundaries following the ingestion of the drug; the difficult struggle to maintain these boundaries, and in some cases at least, their eventual dissolution. Finally, we interpret the tendency toward an increase in the size of the figures as a further indication of the indefiniteness of the body-image boundaries under the influence of LSD-25. In short, we believe that the results of this study are quite consistent with the "body image" hypothesis.

There are, however, two major reservations or qualifications that must be made with respect to our interpretation of the data. We have deliberately limited ourselves to a consideration of the implications of the results for the "body image" hypothesis. In doing so, we have not meant to rule out alternative explanations for the findings. For example, one might attempt to interpret the results in terms of personality dynamics, which provide the customary framework for the interpretation of figure drawings in the clinical setting. Alternatively, at least a portion of the findings are subject to interpretation in terms of impaired intellectual functioning produced by LSD-25 (4). Again, some of the results might be interpreted in terms of the effects of the drug on visual-motor coordination (1). We would certainly not deny the legitimacy and potential fruitfulness of any of these approaches to the data.

Finally, we must admit that in a sense the present study is incomplete. In the circumstances under which the drawings were obtained it was not possible to secure data systematically from the subjects themselves to support our interpretations of the changes that took place in their figures under the influence of LSD-25. We do not know for a fact that the subject who drew the detached limbs had felt his body come apart at the time he produced his drawing; or that the subject who drew the figure with the dissolving body outline was actually having difficulty in telling where his body left off and the rest of the world began; or for that matter, that the few subjects whose figures were virtually unchanged in the drug state were *not* experiencing any marked body image changes when they drew them. From incidental observations made during the course of the study, it seems that this was the case, but the data presently available are not such as prove the point. A study is now in preparation which will attempt to relate changes in figure drawings to verbal reports of the effects of LSD-25 on body image.

SUMMARY AND CONCLUSIONS

Sets of human figure drawings—male, female, and self figures—were obtained from 18 male college graduates under control conditions and at the height of their reaction to 72 mcg. of LSD-25.

1. Judges who had either worked with the drug for some time, or who had had training and experience in the psychodiagnostic use of figure drawings (but not both), were able to differentiate, both reliably and accurately, figures drawn under the influence of the drug from those drawn under control conditions.

2. Figures drawn in the drug state showed

less attention to detail, a greater number and severity of distortions, and more disturbed line quality than those drawn under control conditions. Drug figures also tended to be larger than control figures.

These findings were taken as lending support to the "body image" hypothesis, namely, that human figure drawings are basically representations of the subject's body image. Alternative explanations for the results were mentioned, an important limitation of the study was noted, and further research on the problem was suggested.

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THE FATE OF PSYCHIATRIC CLINIC OUTPATIENTS ASSIGNED TO PSYCHOTHERAPY

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Workers in the field of mental health and illness may delineate within the national population various pools of patients or potential patients. One large pool resides in mental hospitals. These patients have been carefully described many times. Another potentially large pool resides in correctional instutitions across the country. This group has only in recent years been subjected to systematic investigation. A third pool consists of many subgroups which may be lumped together for convenience. Each of these subgroups contains individuals having similar problems of adjustment. They are to be found in various institutions, such as homes for the aged, general hospitals, orphanages, rehabilitation centers, etc., or in special organizations, such as schools or military units. Members of these groups are least likely to come to the attention of a psychiatrist and, except for the military, probably constitute the most sketchily studied pool of all. A fourth group consists of individuals who solicit help from psychiatrists engaged in the private practice of their profession. This is probably the smallest patient pool but it is the one which has been subjected to the most intensive study from the psychodynamic point of view. Hypotheses and findings about the nature and treatment of mental illness based on the study of this group are sometimes generalized to apply to other patient groups as well. In some instances such generalizations may not be warranted without specific determination of their applicability to these other groups. A fifth pool resides in the community but finds its way to various outpatient psychiatric clinics distributed through the nation. This group probably constitutes the largest potential patient pool, but relatively little has been done in the way of systematically studying it.

In this report we are concerned only with outpatients at psychiatric clinics, and of these, only the ones who are assigned to psychotherapy. Psychotherapy is one of the disciplines whose rationale has had its origin and much of its development in the study of the relatively small private patient group. Our intention here is to obtain some evaluation of the effectiveness of psychotherapy with psychiatric clinic outpatients. We shall examine several basic characteristics of this outpatient population, such as sex, race, age, education, income, source of referral, diagnosis, and motivation, with regard to how these are related to psychotherapeutic outcomes. Where possible, we shall compare our findings with those obtained in the few relevant studies known to us (6, 10, 11, 12, 19) in order to evaluate the generality of our findings. All the studies just cited are based on retrospective analyses of clinic records. Our study, in contrast, was planned beforehand, the data collected systematically and concurrently with the investigation. Finally, we shall discuss some implications of our findings.

OPERATION OF THE CLINIC AND COLLECTION OF DATA

It is reasonable to suppose that a patient's course in psychotherapy may be affected by various aspects of his experience at the clinic, so that discussion of these is in order. The method of data collection, which might affect the findings, will also be reviewed.

At the Henry Phipps Psychiatric Clinic, where this study was done, all initial visits

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to the clinic were arranged by appointment,[3] usually by telephone. Patients under 14 years of age were referred to the children's psychiatric clinic. All other patients were given an appointment, usually three to four weeks after the first contact, though it was possible to see some patients more promptly by giving them hours freed by cancelled appointments. Needless to say, nothing could be done about appointment time lost through patients who simply failed to appear without giving notice.[4]

At his initial visit, the patient was seen first by a psychiatric nurse who talked with him to get some idea of his problem and the source of his referral. She indicated the latter on a sheet kept specially for this study by simply checking the appropriate space provided. This data sheet followed the patient to two secretaries who indicated on it the patient's sex, race, age, education and income level, the information being obtained from the patient or the relative bringing him to the clinic. After the patient was thus processed, he was interviewed for about one hour by a third-year medical student (except during the summer months when patients were seen by psychiatric residents or by visiting psychiatrists). Following the interview, the medical student discussed the case with his supervisor, a psychiatrist, who might examine the patient further if he thought it desirable. The psychiatrist determined the diagnosis and disposition, which he indicated on the data sheet.

[3] This does not include some emergency cases, and some stragglers who might be seen briefly to evaluate the severity of their condition and then be given a formal initial appointment for a more thorough evaluation, if indicated.

[4] This description refers to the functioning of the clinic in 1952–1954 when the data were collected. By sending out reminder postcards a week before the appointment and requiring patients to confirm at least 18 hours in advance, the waste of time through missed appointments has now been virtually eliminated and the interval between contact with the clinic and initial appointment has thereby been reduced to not more than two weeks.

Three forms of treatment[5] were offered by the clinic: individual psychotherapy, group psychotherapy and the Continued Treatment Clinic.[6]

In this study we are concerned only with individual psychotherapy. If the patient was referred for this treatment, the medical student and his supervisor discussed it with him, and the supervisor was asked to check his estimate of the patient's motivation for treatment on a three-point scale, included on the data sheet.

Individual therapy was almost always scheduled for one hour a week, though very occasionally a patient might be seen twice as often. The therapy was conducted by psychiatric residents, supervised for an hour a week by a senior psychiatrist. Each resident regularly treated at least six outpatients as part of his training. Although the type of psychotherapy here practiced is probably not correctly classified as either Freudian, Meyerian or Sullivanian, the teachers and supervisors were for the most part representative of these schools of thought.

The common goal of these approaches is to help the patient to function more effectively in his interpersonal transactions and to relieve his symptomatic distress through the medium of a trusting, confidential relationship with his therapist. The therapist strives to maintain an attitude of respectful, consistent and understanding interest as a means of helping the patient to verbalize his problems so that he gains a better under-

[5] In 1954, outpatient electroconvulsive therapy and occupational therapy were also begun, but patients who received these forms of treatment constituted a negligible proportion of the entire patient sample.

[6] In this clinic, patients were seen by a psychiatric resident infrequently for 5 to 20 minutes. The interview was usually confined to how the patient was feeling, and medication was usually prescribed. These brief contacts have seemed to fulfill their purpose of keeping certain chronic patients functioning sufficiently well to be able to remain out of hospital.

standing of them and finds better ways of dealing with them.

The names of all patients referred for individual psychotherapy were placed on a waiting list and assigned in rotation to therapists who had time available. Some of the patients waiting to be assigned to a resident might be seen in weekly interviews by the medical student as part of the latter's required "case study."[7] Occasionally, a psychiatric resident would request a certain kind of patient for psychotherapy to round out his training. The request might be for a male patient, a teen-ager, an ambulatory schizophrenic patient, etc. In these instances, the rotational plan of assignment would be bypassed. Sometimes, too, a patient would be deemed a poor therapeutic prospect by therapists and would have to wait much longer before gaining acceptance for treatment. Occasionally, a resident would interview a patient whom he felt he wanted to treat and would accept him for therapy that very day. These factors influenced the length of wait for certain patients. There was also a seasonal factor, an increased rate of assignment occurring each July when a new group of residents arrived. But in the main, the waiting time between the diagnostic visit and the first appointment for psychotherapy was approximately ten weeks.[8]

A patient was notified of his initial therapy appointment by mail. If he failed to keep it, another appointment note was sent. If the patient again failed to come and did not communicate with the clinic, his name was removed from the waiting list. Some patients called to say that they were no longer interested in receiving the psychotherapy offered. Many of them claimed that they now felt much better and no longer felt the need of it. However, we have not as yet made a systematic study of the reasons patients gave for not accepting psychotherapy when it became available, even though they had previously agreed with the referring psychiatrist to try this form of treatment.

The appointment schedule for each patient in psychotherapy was maintained by a third secretary who indicated on the data sheet each appointment made, kept, and missed. When a patient failed to keep two consecutive appointments, an attempt was made to communicate with him. If he did not respond, or if he indicated his unwillingness to continue in psychotherapy, he was said to have "stopped coming" and was labelled a "dropout" for purposes of this study. When a patient and therapist agreed, however, that there was no longer any forseeable value in continuing psychotherapy, the patient was said to have received the "maximum benefit" to be obtained from the treatment, and this was the discharge category checked by the therapist on the data sheet.

Whether a patient was discharged as "stopped coming" or "maximum benefit," his therapist was asked to indicate his condition at discharge as "improved" or "unimproved." If the patient was said to be "improved," the therapist was asked to state briefly on the data sheet the bases on which the judgment of improvement was made.[9] No attempt was made to have the therapist estimate the degree of such improvement.

FINDINGS

Well over a thousand new patients per year were seen at the clinic during the three-

[7] Interviews with medical students account for an undetermined proportion of the treatment visits reported in the statistical section of this study, and some patients who left treatment after only a few visits were seen only by a student. The medical students received one-half hour of supervision by a senior staff member for each hour of contact with a patient. It is possible that they had a higher termination rate than the resident staff, but there is no reason to think that patients who remained in treatment with them did less well than those seen by the residents (7).

[8] This estimate is based on the analysis of 100 randomly selected cases.

[9] No attempt is being made at this time to evaluate the indices of improvement noted by the therapists.

year period covered by the study. The number seen does not represent the full demand made on the clinic by the community. Some restriction on the number of new patients each day had to be made because of the requirements of teaching and training and the limited though comparatively generous supply of psychiatric personnel available.

The distribution of the entire population sample according to the various characteristics studied can be found in Table 2. However, the task we have set ourselves here does not involve an analysis of the outpatient population *per se*, and so we shall only touch upon a description of it when we discuss the problem of who is selected for psychotherapy. Of more immediate relevance to our problem are the kinds of dispositions made of all new clinic cases, and these are shown in Table 1.

From these dispositions, it can be seen that the clinic outpatient population varied in degree of psychiatric illness from little or none to very marked. Twenty per cent were ill enough to require psychiatric hospitalization. Thirty-five per cent were referred elsewhere because they required no psychiatric treatment, were seen for diagnosis only, or because their income level was too high to make them eligible for the clinic's services. Almost half, or 45 per cent were referred for further treatment at the clinic. This report is concerned only with the 17 per cent referred for individual psychotherapy.

TABLE 1

Types of Disposition: All New Patients

	Per cent
Total new patients: 3413	
Referred to individual psychotherapy:	17
Referred to group psychotherapy:	10
Referred to Continued Treatment Clinic:	18
Total referred for further treatment at Phipps:	45
Hospitalized:	20
Discharged to own care:	18
Returned to referring source:	5
Referred to another facility:	12

WHO IS SELECTED FOR PSYCHOTHERAPY?

For this study, the number in the sample of patients assigned to psychotherapy[10] was 384. This comprised only 66 per cent of patients referred to this form of treatment, since a large number of patients were in therapy when the data were collected for tabulation and an additional number were still on the waiting list or had not yet had their first appointments. Some who were already discharged had not yet been evaluated by their therapists and were therefore also excluded from the sample.

Table 2 and Figure 1 summarize the data with regard to the frequencies of certain characteristics of patients whom the psychiatrists referred for psychotherapy.

It will be seen that, at the Phipps Clinic as elsewhere (13, 15, 19), psychiatrists tend to refer for psychotherapy persons who are most like themselves. Thus they referred significantly more white than Negro patients, the better educated, and those in the upper rather than the lower income range.

Figure 1 shows that there is almost a straight-line relationship between educational level and frequency of referral for psychotherapy. There is also a decided preference for self-referred patients and those referred from other psychiatric sources, as compared with patients sent from other Hopkins clinics. These preferences all accord with the hypothesis that psychiatrists consider as good candidates for psychotherapy those patients with whom they can more easily communicate and who share their value systems.

The slight and statistically questionable tendency to refer more women than men for psychotherapy may simply reflect that more women than men are willing to take time for psychotherapy, since for women this less

[10] For brevity, we shall use the term psychotherapy to refer to individual psychotherapy, except where explicitly stated otherwise.

TABLE 2

Who Is Selected for Psychotherapy?

Category	Subgroups	Per cent expected* (N = 3413)	Per cent obtained (N = 384)	Level of significance
Sex	Male	42.8	38.5	.10
	Female	57.2	61.5	
Age	14–19	12.4	18.0	.01
	20–29	27.5	37.8	
	30–39	29.0	28.6	
	40–49	17.0	10.1	
	50–59	8.5	4.2	
	60+	5.6	1.3	
Race	White	69.4	81.3	.01
	Negro	30.6	19.7	
Education: grade level reached	0–4	12.0	2.1	.01
	5–8	36.2	25.9	
	9–12	40.9	51.7	
	College	10.9	20.3	
Annual income	DPW	17.1	3.6	.01
	−$1,000	7.1	5.2	
	−$2,000	12.0	14.2	
	−$3,000	18.6	23.8	
	−$5,000	35.5	37.3	
	$5,000+	9.7	15.8	
Source of referral	Steering Clinic	21.9	14.1	.01
	Other JHH clinics	18.1	14.6	
	Medical sources	20.0	21.6	
	Psychiatric sources	8.1	12.7	
	Social agencies	4.9	4.3	
	Courts	1.1	1.1	
	Interested others	14.9	15.7	
	Self	11.1	15.9	
Diagnosis† n = 367	Psychosis	44.2	19.4	.01
	Psychoneurosis	43.2	64.8	
	Personality disorder	12.7	15.8	
Motivation‡ n = 161	High	33.3	38.0	.01
	Moderate	33.3	45.9	
	Low	33.3	16.1	

* The term "expected" refers to the percentage of all *new* patients in the total sample who fell in the subgroup indicated. "Obtained" refers to the percentage of all patients in the total sample of *referred* patients who fell in that subgroup. The significance of the difference between expected and obtained was tested by the chi-square method.

† For purposes of comparison we have taken some liberties: we have combined several diagnostic categories to make three major groups called psychoses, psychoneuroses, and personality disorders. The psychosis group includes some organic and affective cases, but most are schizophrenic. The psychoneuroses and personality disorders include the usual subgroups. The less frequent diagnostic categories such as habit disorder, adolescent reaction, psychophysiological disorder, et al. were eliminated from the calculations involving diagnosis, reducing the N for these statistics by 17. Patients who were said to have both a psychoneurotic and a character disorder were counted in both categories. This results in comparing a few individuals with themselves which may slightly blur the picture, but should not obscure gross differences between groups.

TABLE 2 *Continued*

‡ Only 161 or 42 per cent of all patients referred for psychotherapy were rated by the psychiatrists according to degree of motivation. Since this rating was to be made only for referred patients rather than routinely for all patients, and since this category was badly placed on the data sheet, psychiatrists simply forgot frequently to make this rating. There may have been some reluctance, too, to try to rate some of the more difficult cases, but we were not aware of such a factor. The sample rated seems to be representative of the entire group referred in various categories checked, such as age, sex, etc. Since we found nothing to indicate that the sample was biased and since the size of the sample was still large, we decided to analyze this category along with the others. Since we did not know the distribution for the subcategories of motivation in the general population of new patients, we assumed equality for purposes of statistical comparison. However, we believe that the low group would be proportionately much higher and the high group much lower in the total new-patient population.

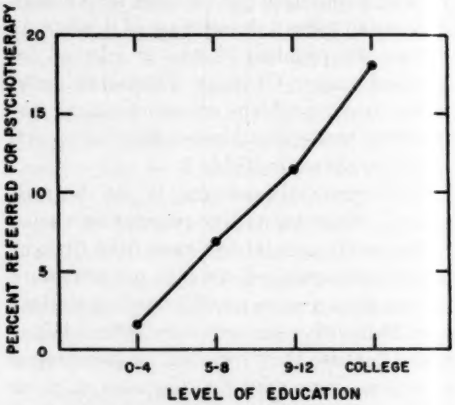

FIG. 1. Frequency of referral for psychotherapy according to level of education.

often involves loss of income, or the necessity of making special arrangements.

Patients in the 30 to 39 year age bracket are referred in proportion to their number, whereas there is a decided preference for patients who are younger and a lack of preference for older patients. This probably reflects the often heard opinion that younger people are better therapeutic risks since their illness is not as "fixed," as well as the opinion that one receives a greater return on one's investment of time if a younger person with his whole life ahead of him gets well, as compared to an older person whose life is in good part behind him.

Psychotic patients were least likely to be referred and psychoneurotic patients most

likely, whereas patients with personality disorders were referred in approximate proportion to their number. At least part of the low referral rate for psychotic patients can be explained simply on the grounds that a large number of such cases had to be hospitalized. However, such cases also involve greater risk and are often thought to be more difficult to treat successfully, whereas psychoneurotic patients are usually thought to be potentially the most responsive to psychotherapy.

Patients judged to have poor motivation were least likely to be referred, in keeping with the commonly held but unproved (3, 8, 9) opinion that motivation is an important factor related to success of psychotherapy. There are at least two possible explanations for the fact that the absolute number of "moderate" patients is larger than the number of "high" patients. One is that there may have been fewer highly motivated patients in the new-patient population generally. The other is that therapists in judging this attitude may have tended to favor the middle of the scale over the extremes.

WHO FAILS TO ACCEPT PSYCHOTHERAPY WHEN IT BECOMES AVAILABLE?

Of the 384 patients referred for psychotherapy, 130 or 35 per cent failed to accept it when it became available.[11]

Table 3, column 3 presents the frequencies for the various population characteristics of refusal to come for psychotherapy when an appointment could be arranged. The percentages of those who refused to accept psychotherapy were not significantly different for men and women, Negro and white, or patients in the different diagnostic categories. Expectations one might have had that psychoneurotic patients would be more willing to accept psychotherapy than psychotic patients or patients with personality disorders, were not borne out. Neither was age a significant factor, although it is interesting to note that patients aged 30 to 39 had the lowest rejection rate and that this rate became progressively higher for the age groups both above and below that.

Source of referral, however, did make a difference. Patients who were referred by a psychiatrist or psychiatric installation were more likely not to refuse therapy. The zero rejection rate for court-referred cases is based on only four cases. These patients were obliged by legal pressures to come to treatment. Self-referred patients had about the same refusal rate as those referred from medical sources. Patients who had been referred to the clinic by a social agency or the Steering Clinic were most likely to refuse therapy, suggesting that they had felt pushed into a psychiatric clinic and into agreeing to psychotherapy against their own wishes. Motivation in such cases would not be high, and it can be seen that patients with low or moderate motivation had the higher rejection rates.

Social class factors also made a difference with regard to acceptance of therapy. Patients of lowest educational and income levels were most likely to refuse psychotherapy when it became available. This finding complements the finding of the Yale group that psychiatrists tend to reject patients of the lower classes for psychotherapy (14). The rejection appears to be mutual.

[11] It was thought that the length of wait for therapy would influence the rate of rejection. To check on this possibility, the records of 100 patients who had been referred for therapy were selected at random from the files. Of these, 36 did not keep their therapy appointments. This compares favorably with the 35 per cent rejection rate obtained for all referred patients, indicating that the sample is probably representative. For all 100 patients, the median length of wait was 68 days, the distribution skewed toward the higher end of the curve. The median length of wait for those accepting therapy was 69.5 days as compared to 64.0 days for those rejecting therapy. The groups were quite comparable in this respect, the slight difference between them not statistically significant.

TABLE 3

*Refusal, Length of Stay and Improvement According to the Population Characteristics Studied** (N = 384)

Category	Subgroups	Failing to accept psychotherapy when it becomes available		Staying in psychotherapy six or more hours		Per cent judged improved	
		Per cent	Level of significance	Per cent	Level of significance	Per cent	Level of significance
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sex	Male	34	NS†	67	.01	38	NS
	Female	35		45		44	
Age	14–19	41	NS	43	NS	38	NS
	20–29	33		57		46	
	30–39	30		51		36	
	40–49	37		50		47	
	50–59	38		77‡		33	
	60+	40					
Race	White	33	NS	59	.01	42	NS
	Negro	39		31		42	
Education	0–8‡	44	.10	37	.01	44	NS
	9–12	33		61		41	
	College	30		63		50	
Annual income	DPW	50	rho =	42‡	NS	35‡	NS
	−$1,000	40	−.83;				
	−$2,000	38	p =	47		32	
	−$3,000	40	.02	67		46	
	−$5,000	32		53		39	
	$5,000+	30		61		48	
Source of referral	Steering Clinic	48	.01	26	.02	36	NS
	Other JHH clinics	37		38		33	
	Other medical	34		60		45	
	Psychiatric	17		65		43	
	Social agency	63		50		25	
	Court	0		25		33	
	Interested others	33		54		33	
	Self	37		65		46	
Diagnosis	Psychosis	29	NS	54	NS	39	NS
	Psychoneurosis	34		55		43	
	Personality disorders	35		52		35	
Motivation	Low	42	.01	40	NS	54	.06
	Moderate	51		61		22	
	High	28		68		43	

* To test whether the frequencies of occurrence among the subgroups in each category were significantly different from one another, chi-square was the statistic used. To determine if income level and refusal to accept psychotherapy varied together the rank-order correlation method was used.

† NS = Not Significant.

‡ The educational subgroups 0–4 and 5–8 were combined because of the small number referred in the 0–4 group. The income subgroups DPW and −$1,000 were combined because of the small number of patients having no income, and the age subgroups 50–59 and 60+ were combined because of the small number of patients over 60.

WHO STAYS IN PSYCHOTHERAPY?

Of the 384 patients referred for psychotherapy, 254 or 65 per cent came to at least one therapy session. The distribution of their attendance is given in Table 6, which will be discussed later. It seemed of interest to examine the characteristics of patients who stayed in psychotherapy, since this group is clearly contrasted with those who refused to return for even one session. For statistical purposes, attendance at six or more sessions was selected as the criterion for staying in treatment, since about half the patients who entered therapy had less than six hours, and half six hours or more.

Table 3, column 5 summarizes the distribution of characteristics of the patients who stayed for six or more treatment hours.

Sex was one factor related to duration of treatment, males being more likely to have six or more hours than females. This finding was not predicted and no reason for it is offered.

The social class triad of factors was an important determinant of duration of treatment, a finding which corroborates the report of the Yale Group. Only three of every ten Negro patients, as compared to about six of every ten whites, had six or more hours of therapy. Similarly, only slightly more than one of every three patients with zero to eighth grade education had six or more hours, in contrast to about two of every three with nine or more years of education. Income as a factor did not reach the level of statistical significance found in race and education, but did approach it and was in the expected direction.

Source of referral was also related to duration of treatment. Patients who were referred by other psychiatric sources or who were self-referred were the ones who most often had six or more hours of therapy, whereas patients referred from the Steering Clinic and other clinics in the hospital were the ones who most often had less than six hours.

Motivation may also have been a factor affecting length of stay in treatment, although the differences between subgroups did not quite reach the five per cent level of significance. Only two of every five patients with motivation appraised as low had six or more hours as compared to two of every three patients with high motivation. There is a suggestion, too, that those in the teen-age group were most likely to have the briefest duration of treatment whereas the oldest patients were most likely to have at least six hours of therapy. However, the difference between age groups when all groups were considered was not statistically significant. Diagnosis was clearly not at all related to duration of treatment.

Comparison of Table 2 with column 5 of Table 3 shows that most of the characteristics of patients which led psychiatrists to refer them for psychotherapy also predisposed them to remain in treatment. These characteristics include race, education, income and source of referral. There were two clear exceptions to this, however. More women were referred but more men stayed; more psychoneurotic patients were referred, but they showed no greater tendency to stay in treatment than patients in the other diagnostic categories.

Comparison of columns 3 and 5 of Table 3 shows the expected inverse relationship between refusal to accept treatment and length of stay in it, with respect to socioeconomic indices and sources of referral.

WHO BENEFITS FROM PSYCHOTHERAPY?

As will be seen from Table 4, 42 per cent of the patients who began psychotherapy were rated by their therapists as improved at the time of termination of treatment.[12] Table 3, column 7 lists the frequency dis-

[12] The other data in Table 4 are considered below.

TABLE 4

The Discharge Status of Patients Receiving Psychotherapy (N = 216)

	Per cent
Maximum Benefit:	25
Stopped Coming:	75
Improved:	42
Unimproved:	58
Maximum Benefit, Improved: (All patients beginning psychotherapy)	17
Maximum Benefit, Improved: (All patients assigned to psychotherapy)	9

* Of the 254 patients who began psychotherapy, 34 were transferred and 4 were hospitalized. These patients were not rated as improved or unimproved (although one might assume that the four cases requiring hospitalization were unimproved) and they were not included in evaluations of improvement for the sample as a whole.

tribution of characteristics of patients in relation to whether they were so rated.

Of the eight characteristics studied, only motivation approaches an acceptable level of statistical significance with regard to the frequency of judged improvement for the various subgroups. However, it was the low motivation group which had the highest rate of improvement, contrary to expectation, while the group with moderate motivation had by far the lowest improvement rate.[13]

Though no other trends were statistically significant, most were in the same direction as those related to referral for therapy. The better educated and economically better off may have shown more tendency to improve than those less favored in these respects. Psychoneurotic patients and patients referred by themselves or by other psychiatric or medical sources showed a tendency to improve more often than those with other diagnoses or who were referred from other places, but the differences are not statistically significant. Contrary to what might have been predicted on the basis of commonly accepted criteria for the selection of patients for therapy, age failed to show a consistent trend with respect to improvement rate, as it had also failed to do with respect to staying in treatment (Table 3, column 3).

[13] It might be that patients with low motivation were referred for treatment only if the psychiatrist thought they possessed other favorable prognostic qualities of sufficient strength to outweigh this drawback.

DISCHARGE STATUS AND LENGTH OF PSYCHOTHERAPY

To this point we have considered the clinic's psychotherapy program from the standpoint of characteristics of the patient population in relation to referral for treatment, refusal or acceptance of it, and improvement under it. The data presented in this section bear on the overall efficiency of the treatment program as revealed by some relationships between discharge status and length of psychotherapy.

It will be recalled that psychiatrists were asked to rate their patients in two ways when they terminated clinic contact. If the patient stopped without notifying the therapist or without the latter's consent, he was rated as "stopped coming." If both agreed that no further benefit was to be gained from treatment, he was rated as "maximum benefit." In addition, the therapist was asked to rate each patient as "improved" or "unimproved." The division of discharged patients according to these categories is summarized in Table 4.

Three of every four patients were said to have "stopped coming," that is, to have dropped out of therapy without the therapist's consent. Approximately, three of every five patients were discharged as unimproved by their therapists. Assuming that the optimal discharge status accorded was maximum benefit: improved, we note that only 17 per cent of all patients who received psychotherapy were so discharged. We have also asked ourselves how successful our psychotherapy program has been in terms of service to the community. One indication of this would be to ask how many patients who were referred for psycho-

therapy received the optimum discharge evaluation of maximum benefit: improved. The answer is nine per cent, or about one of every 11 patients referred.

Table 5 demonstrates that whether a patient is discharged as having received maximum benefit or as having dropped out of treatment makes a difference with regard to his being rated improved or unimproved. About two of every three patients who dropped out were said to be unimproved as compared to about one of every three patients discharged with a "maximum benefit" rating.

Table 6 presents the duration of psychotherapy for all treated patients. It can be seen that almost half the patients received only five hours or less. One of every five patients received 6 to 10 hours of psychotherapy, and only one patient in six had more than 20 hours. Dropouts contribute largely to this pattern of therapy duration. More than half of the patients discharged as "stopped coming" dropped out in the first five hours. This suggests some feeling of disappointment or anxiety in these patients regarding their early experience with this form of treatment. That this constraint persisted for some patients is suggested by the fact that more than a quarter of the dropouts occurred after the eleventh hour. The fact that so many patients ended therapy after so many sessions without first discussing this termination with their therapists suggests that the relationship between them had not reached a stage of great trust and confidence.

Finally, there remains to be considered the relationship of judged improvement to duration of psychotherapy. It will be seen from Figure 2 that the per cent of patients judged improved increased up to 20 sessions and then declined. The number of cases with more than 20 hours of treatment is too small to permit determination of whether the improvement rate rises again, remains stable, or declines further for therapy of greater duration.

TABLE 5

Relation Between Dropping Out of Psychotherapy and Judged Improvement (N = 216)

	Per Cent Improved	Per Cent Unimproved
Stopped Coming	34	66
Maximum Benefit	63	37

Chi-square = 12.62, P = .01.

TABLE 6

Duration of Psychotherapy

	Number of hours:			
	1-5	6-10	11-20	20+
Per cent beginning psychotherapy	47.2	18.9	17.0	17.0
Per cent discharged "stopped coming"	53.7	18.5	14.2	13.6
Per cent discharged "improved"	32.5	20.5	28.9	18.1

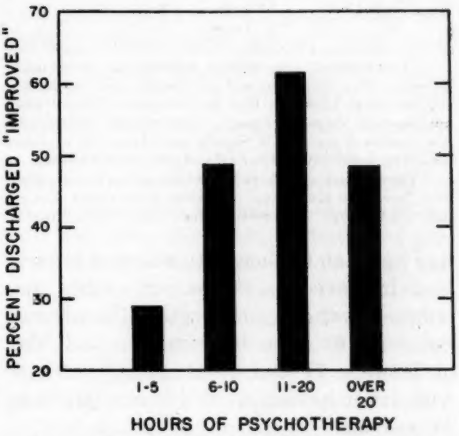

FIG. 2. Frequency of judged improvement according to duration of psychotherapy.

We may obtain some idea about the contribution of psychotherapy to the amount of improvement found by considering only cases judged improved and asking how much psychotherapy these patients had. It can be seen in Table 6 that approximately one third of all patients judged improved had only five or less hours of psychotherapy, and that more than half

TABLE 7

Length of Psychotherapy of Psychiatric Clinic Outpatients

Authors	Locus of study	No. of cases	Per cent of patients returning for different numbers of treatment visits			
			1–4	5–9	10–19	20+
Garfield & Kurz	VA, Milwaukee	560	43	24	20	13
Schaffer & Myers	Yale	183	52	15	33	
			1–5	6–10	11–20	21+
Kurland	VA, Baltimore	1749	51	49		
Rosenthal & Frank	Phipps, Baltimore	254	47	19	17	17

TABLE 8

Rate of Improvement for Psychiatric Clinic Outpatients

Authors	Locus of study	Number of cases	Per cent improved	Per cent unimproved
Myers & Auld	Yale	47	34	66*
Ginsburg & Arrington	N.Y.C.	150	19	81†
Rosenthal & Frank	Phipps	254	42	58
Menah & Golden	VA, St. Louis	575	39	61

* "Unimproved" cases include patients said to be unimproved by their therapists, and patients who quit psychotherapy, the authors inferring that the latter group did not profit from therapy. Transferred cases are not included. This population consists of the cases of Schaffer and Myers (19) who were treated by senior psychiatric staff and psychiatric residents.

† These figures are not stated by the authors but are calculated from some figures cited in the text of the article. The authors use the term "unsuccessful" rather than "unimproved."

had less than ten hours. It is also of interest that improved cases are not evenly distributed over different lengths of treatment, but tend to have between one and five, or between 11 and 20 treatment sessions, with fewer having six to ten or more than 20 sessions.[14]

DISCUSSION

The striking aspects of this overview of the functioning of a psychiatric clinic are the failure of many patients to accept psychotherapy, and the relatively poor results of psychotherapy in patients who do accept it. We have no reason to believe that the psychiatrists at the Phipps Clinic are less competent or that the treatment program is less well conducted than at other similar clinics, and such data as are available from other installations confirm this.

A complete review of published data from other clinics is not attempted here since few give sufficient data to permit adequate comparison. Only the studies tabulated in Table 7 make clear that patients who were offered treatment but did not accept it are excluded from the statistics. The others are ambiguous in this regard. Garfield and Kurz (6) and Kurland (10) give data separately for patients who did not return for the first treatment visit, and the percentages are similar to the Phipps figures, being 29 per cent in both studies as compared to 35 per cent in the Phipps series.

The data in Table 7 indicate that the experience of other clinics with respect to duration of treatment contact is closely similar to ours. The percentages of those stopping before the fifth or sixth meeting range from 43 to 52, and the percentages of those coming for various longer periods are likewise similar.

The Yale Clinic, which, being part of a teaching hospital, would be expected to be most comparable to Phipps, shows a startlingly similar distribution of treatment visits. Fifty-two per cent of their patients stopped in less than five visits; 47 per cent of ours stopped in less than six. Thirty-three per cent of the Yale patients had more than 10 visits; 34 per cent of the Phipps patients had more than 11 visits.

Data with respect to improvement are even more sparse and difficult to compare than those concerning length of treatment. Table 8 presents such data as are available. Our clinic reports the highest rate—42 per cent—and this could hardly be called a source of gratification. All these rates are below the expected two-thirds improvement rate found in most reports of psychotherapy with non-clinic patients (1). Poorer improvement rates from clinics than from

[14] Cartwright (2) and Taylor (22) report a similar "failure zone," but found it to occur between approximately the 13th and 21st treatment sessions in two different series.

other settings were already noted in 1945 (23).

The evaluation of these data is complicated by the possibility that standards by which therapists or other judges evaluate improvement may be too severe. At least one study suggests that they are less favorable than patients' self-ratings.[15] If this is actually so, it could be attributable in part to raters' tendencies to equate improvement with a patient's ability to verbalize why he is better in the therapist's language ("insight"). Almost all therapists in psychiatric clinics are in private practice or are preparing for it, and the conceptual model for private psychotherapy is that it is a prolonged relationship which is not successfully completed until the patient has achieved insight into the relation of his complaints to past and present interpersonal problems. This preconception is reflected in our data in that it leads psychiatrists to refer for therapy patients who they believe are most likely to achieve this kind of therapeutic goal, *viz.*, those whose socio-economic and educational levels are closest to their own. These criteria seem to predict fairly well who will stay in therapy—namely, those who get along comfortably with their therapists—but, at least in our study, they show no clearcut relationship to improvement. This should prompt us to reevaluate the emphasis on insight-based therapy with such patients.

The same conceptual model accounts in part for the tendency for therapists' ratings of improvement to be correlated positively with the length of treatment (20, 21). The implicit assumption is that genuine, *i.e.*, permanent, improvement can only occur as a result of the insight gained through long-term therapy, all other amelioration in a patient's condition being symptomatic, superficial, and temporary. The fact that about one-third of the patients judged as "improved" had had five or less psychotherapeutic sessions, however, suggests that the psychiatrists recognized that some patients could achieve considerable insight quickly, or that on occasion they used criteria of betterment other than insight.

Even with every allowance for the possibility that therapists' estimates of patients' improvement may be low, the improvement figures reported by psychiatric clinics point to the desirability of reexamining the implicit assumption on which outpatient psychotherapy rests.

The ultimate aim of all psychotherapy, as of any other healing art, is to help a patient feel better and function better, and the routes to these goals probably differ considerably depending on the nature of the particular patient and his problem. From the standpoint of psychotherapy, common to all psychiatric patients are chronic difficulties in getting along with others, so that psychotherapy, to be successful, requires some change in the patient's interpersonal attitudes and behavior.

Through one means or another, these changes are produced by influences exerted by the therapist. Techniques which facilitate the gaining of insight represent one mode of beneficial influence, but by no means the only possible one. The patient's mere belief that he is being helped may be sufficient to raise his morale to the point that he can initiate beneficial changes in his relationship with others, and there is growing reason to think that relief brought about by a brief contact with a therapist which mobilizes the patient's expectancy of help need not necessarily be transient (4, 5, 16).

Experimental models of acquisition and extinction of behavior have given rise to techniques (17, 24) which may involve hypnosis, relaxation, suggestion, and desensitization, and which appear to bring about rapidly effective changes in the behavior patterns of some patients. Many other

[15] Lorr, M., Progress and Problems in Research on Psychotherapy, paper read at the V.A.-University Conference, University of Maryland, November 14, 1957.

variations of hypnotic technique have been claimed to produce good results. Strong emotional abreactions induced, for example, by ether (18) may bring about a beneficial reorganization in the attitudes of certain patients.

The problem is that we have only the most tenuous notions as to which types of treatment are most useful with what types of patients and conditions. We need more knowledge of such ill-understood factors as the part played by the patient's faith in treatment and aspects of the therapist and situation which affect this, and a better understanding of the application of established psychological principles of learning, group dynamics, self-concept and social influence to the therapeutic process.

Eventually one may hope to develop a battery of diagnostic and treatment methods which will make possible a rational selection of different types of treatment for the different types of patients described in the introduction to this paper. The first step towards the realization of this hope would be a willingness to experiment more freely with various therapeutic approaches already proposed, under as carefully controlled conditions as are possible, in different treatment settings.

SUMMARY

Insight-based psychotherapies seem to be less effective with psychiatric clinic outpatients than with patients in some other types of setting, even though psychiatrists mostly refer for psychotherapy those clinic patients whom they deem most likely to benefit from such treatment, *viz.*, young psychoneurotic patients with relatively higher socio-economic status and education who are relatively better oriented and motivated toward receiving such treatment. In a study done at the Henry Phipps Psychiatric Clinic, approximately one of every three patients referred for psychotherapy failed to accept it when it became available, even though he had previously agreed to try it. Those of lower social class and motivation were least likely to accept it or to remain in psychotherapy once they tried it, but generally obtained as much benefit from it as those of higher social class and motivation. Three of every four patients who began psychotherapy terminated without discussing this step with their therapists. Approximately half of all patients had five or less hours of therapy and about six of ten were discharged as unimproved. Other clinics report similar experiences. It is pointed out that insight-based forms of psychotherapy may not be the best ones for psychiatric clinic outpatients and that the time may be at hand for wider experimenting with other kinds of psychotherapy which have shown evidence of being adaptable with success to a clinic outpatient population.

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WHAT HAPPENED IN THERAPY AS SEEN BY THE PATIENT AND HIS PSYCHIATRIST[1]

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Psychiatric literature is replete with histories of patients who improved following a period of psychotherapy. The fact that they did actually improve is confirmed by their performance, their attitudes, and their behavior following the termination of therapy. The reasons why psychotherapy helped, the significant insights gained, and the other therapeutic mechanisms which were effective, are usually included in such case histories; but these are uniformly spelled out from the psychiatrist's viewpoint, and confirmation or cross-validation which might tend to corroborate the therapist's own formulation is rarely included. This paper is intended to suggest a means by which the understanding of what goes on in therapy may be broadened and made more accurate.

Two students, who made significant improvements following short-term, psychoanalytically-oriented psychotherapy at the Harvard University Health Service Psychiatric Clinic, were seen following the termination of their therapy with a psychiatrist by the psychologist who had originally tested them, and were asked by him to describe what it was about the therapy just concluded which had helped them. This description was then matched against a similar one prepared by the psychiatrist, in which he described what he considered to have been the significant elements in the therapy.

The method was as follows. A letter invited the two men in to discuss *how* we had been helpful. The interview began in a very nondirective manner, with the psychologist first raising in turn each of the general topics mentioned in the psychiatrist's summary and then testing the patient's awareness of the specific events the psychiatrist had recorded. After so bracketing the target with open-end leads, the interviewer finally asked direct questions on each point concerning insight and new self-awareness.

The first student, Sam P., was a sophomore who had consulted the University chaplain because of an ethical conflict regarding his fiancee, Jane. In the course of the first counselling interview, the chaplain asked some questions about Sam's parents, whereupon Sam immediately burst into tears. The chaplain referred him to a psychiatrist, and Sam told of his embarrassing habit of crying suddenly and frequently when talking with his contemporaries, his tutors, or faculty advisors, and particularly when in the presence of his fiancee. It was for this symptom that he principally wanted help. He was seen for psychotherapy over a period of approximately seven months, at once-a-week intervals for an hour. At the end of that time, he was no longer troubled by crying spells, was doing markedly better in his academic work, felt more secure and was found to be more sociable and easy to get along with.

The early part of treatment concerned itself with Sam's relationship with his parents and theirs with each other. Sam expressed a great deal of resentment against his mother for her aggressive, dominating attitude towards his father, and finally said that he felt that she had seriously undermined his father's sense of strength and integrity, as well as destroyed any relationship which there might have been between

[1] Presented at the Eastern Divisional meeting, American Psychiatric Association, New York, November, 1957.

[2] Harvard University Health Service.

father and son within the family. He then made the jump between his mother and Jane, saying that he could see that he probably distrusted Jane unconsciously, as much as he had his mother. He went on to discuss his feelings of resentment against his parents for being overly demanding in their expectations so far as he was concerned. This culminated in an angry outburst while he was visiting at home, during which for the first time he lost his temper with them and accused them of being overly rejecting and cold in their dealings with him. On his return to college, he spoke frankly about his passive needs, stating that on the one hand he felt guilty because he needed so much, and on the other hand felt angry because people did not fulfill his needs.

His crying spells became somewhat less after this, but he was still troubled by them when with Jane. One night he demanded an emergency interview with his therapist. He was exceedingly overwrought, alternately weeping and shouting in anger against Jane because she had refused to have intercourse with him and had suggested that they terminate their engagement. He continued talking in this manner for over an hour, and then suddenly said, "I don't know why I think of this now, but for the first time I remember some sex play I had with my sister when I was six." Immediately after saying this, he felt calm enough to return to his room, where he went to sleep.

In the interviews following this dramatic revelation, Sam discussed in some detail his relationship with his mother, dwelling particularly on the seductive aspects of her behavior, such as her allowing him to wash her back in the bathtub. He also began having hypnagogic images of enjoying sex play with her. Although this coming to the surface of unconscious material frightened Sam at first, he later came to accept these feelings as being normal, and went on to express again some of the strong negative feelings he had towards his mother, picking up a phrase from one of his T.A.T. ing stories, "witch-mother," and elaborating upon it. He said that he now realized the strong positive and negative feelings which he held toward his mother, and stated that he could reconcile himself to them and had come to realize that they were natural and nothing to feel guilty about.

He showed further improvement after this, and went on to ask if the psychiatrist would be willing to see Jane, stating that he was now seriously concerned about her emotional state of mind. I found her to be a confused girl, but one who was basically very attached to Sam, dependent on him in many ways, and genuinely confident about their marriage being a success. I communicated this to Sam, and the reassurance which this gave him seemed to result in further symptomatic gain.

Shortly after this, Sam began talking about how he had formerly felt totally subservient to his parents and bound to them by his obligation to them for the many things they had done for him. In the next interview, he suggested that he might terminate therapy. It seemed to the psychiatrist that Sam was testing him out to see whether or not he was going to hold him to some obligation, as he had felt his parents had. He was allowed to terminate his formal therapy at that time, and returned only on two occasions following this, each time to go over some of the material which had been previously discussed in therapy.

Table 1 presents a comparison between the therapist's view of what happened in the course of this therapy, and what the patient reported his impression to have been.

The second patient, William C., was a 24 year old graduate student in engineering, who came directly to the Psychiatric Clinic complaining of acute anxiety attacks occurring during almost every lecture. These symptoms had begun several weeks earlier

TABLE 1

Comparison of Psychotherapist's and Patient Sam's Views of Significant Therapeutic Events

	Therapist	Patient Sam P.
Significant insights	Recognized transference of distrust from his mother to Jane.	Gained a truly objective picture of Jane which included both her faults and her strengths. No mention of transferred distrust.
	Recognized the degree of repressed anger against parents.	Gained a truly objective picture of his parents which included a concept of them as weak and neurotic. No mention of anger.
	Awareness of his mother's seductive and overprotective attitudes during his childhood as well as at present.	Came to realize Mother had been overindulgent as well as seductive.
	Not mentioned.	Recognized that he had felt totally obligated to parents and that he could be free of this.
Turning points in Therapy	Recollection and description of sex play with sister in emergency interview.	Support given by therapist by his granting emergency interview. No mention of sex play.
	Interview with Jane by therapist.	Not mentioned.
	Emotional outburst while visiting home.	The support gained from visit with parents.
Material originating from the patient thought to have been therapeutic.	Description of sex play.	Not mentioned.
	Describing hypnagogic images of sexual intimacies with mother.	Not mentioned.
Material originating from the therapist thought to have been therapeutic.	Discussion of the existence in the unconscious of passive "needs", certain incestuous wishes and large amounts of irrational hostility and the normal manifestation of these in everyday behavior.	Not mentioned.
	Not mentioned.	Therapist stating that there must be a reason for his symptoms.
	Not mentioned.	Therapist read the words "Witch Mother" from the test report.
Transference factors thought to have been therapeutic.	Authority can be accepting of him despite his demandingness.	Authority gives sanction to many of his attitudes and understanding them does not reject him.
	Not mentioned.	The therapist could give him help and support but still let him go away independently when he wished to.
General picture of what happened.	As a result of insights into oedipal feelings past and present, the recollection and description of certain childhood incidents and the correlation of these with present-day problems the patient was relieved of symptoms.	As a result of gaining an objective picture of myself, my parents, and my fiancee through the eyes of an impartial and respected individual who did not encompass me as my parents did, I was able to function more happily and efficiently.

and were growing progressively more severe. It had come to the point where he was frightened to go into a classroom, and he had been forced to cut so many classes that he was in danger of failing out of school.

The student's father had died a year and a half previously; he had been a prominent lawyer in a large city, and had accumulated a sizable fortune. For the three years prior to his death, however, the father had suffered from slowly progressing cerebral arteriosclerosis which had caused him to be depressed, and over the last year almost completely irrational. He had lived on the fourth floor of their city home in a small room, alone with his dog, cooking his meals in an open fireplace. Whereas formerly he had been an exceedingly proud, rather rigid and authoritarian individual, during the last few years of his life he had become maudlin, pathetic, and had clung to his son, Bill, in a puppy-like way. Bill's mother was a haughty, vain woman; she treated everyone around her as a menial, and during her husband's illness she completely ignored him and carried on promiscuously with other men, with the full knowledge of her son but not of her husband.

During the first interviews, Bill dwelt entirely upon his relationship with Claire, a nymphomaniac friend of his with whom he had been having an affair over the last eight years. He had no respect for the girl, and had tried to terminate the relationship on many occasions. His father had known about Claire, and five years previously had made Bill promise that he would never see her again. He had continued to do so, however, without his father's knowledge. He felt that in doing so, he was both being disloyal to his father, and at the same time defying him. He realized that now that his father was dead, he should be able to terminate this relationship, but he had been completely unable to do so. In the week before he began therapy, Bill had made another attempt to stop communicating with Claire, but it had ended in failure after she had written him that she was planning to marry someone else. The thought of this so distressed Bill that he called her immediately and arranged for a date. Although he realized that the therapist could not bring about a magical resolution of this problem, he needed to talk about it.

Gradually the emphasis shifted from a discussion of Claire to a description of his suicidal fantasies and his fears about the nature of his illness. He said that he had understood from magazine articles he had read that anxiety could lead to paranoia, and that paranoia in turn could develop into schizophrenia, which, he envisioned as an incurable, progressively deteriorating disease. The therapist discussed the nature of anxiety, and the distinction between a neurotic and a psychotic disorder. Psychological tests were given, and the results were explained to him in considerable detail. Since they conclusively showed that he was not psychotic nor in danger of becoming so, he felt enormously relieved.

No relief from his anxiety during lectures occurred at this time, however. The therapist then focused the interviews on Bill's feelings about his father's death. After discussing the cold, school-masterly attitude which his father had displayed toward him originally, Bill discussed the awkward, dependent quality of it during the last years of his father's illness. He went on to describe the sordidness of the final days of his father's life, and finally told of the hopes that he had harbored that his father would die quickly, and have it all over with; and also of his own guilt about having had these feelings, as well as his present guilt about the things which he felt he might have done which could have prolonged his father's life. At a later point in the same interview, he spoke of similar death wishes toward his father which he had experienced

when he was younger, and felt that his father was being unreasonably harsh. The day following this interview, the patient noted that his anxiety in lectures was far less, and when he came for his appointment the next week, he said that he was "90 per cent cured."

He went on to discuss the resentment he felt toward his mother for her treatment of his father, and also his anger at her for the humiliating experiences which she forced Bill to go through; for instance, insisting that he punch a taxi-driver who, she felt, had overcharged her. As he talked about

TABLE 2

Comparison of Psychotherapist's and Patient William's Views of Significant Therapeutic Events

	Therapist	Patient Bill C.
Significant insights	That he need not feel guilty over the unconscious death wishes he had had towards father.	Not mentioned. (Denied having had any hostile feelings toward father.)
	His unconscious hostility towards authority figures at present was controllable.	Not mentioned
	That his conscious feelings of hostility to mother were justifiable.	No mention. (Patient did not describe anything that could be called insight but attributed his improvement to "outside forces" and the work of the therapist in "focusing the discussion.")
Turning points in therapy	Discussion of test results.	Not mentioned as a turning point.
	Discussion of hostility to father.	Not mentioned.
	Discussion of hostility to mother.	Not mentioned.
	Not mentioned as a turning point.	Finding out that he was not irrevocably bound to Claire.
Material originating from the therapist thought to have been therapeutic	Information about the nature of neurosis.	Information about the nature of *his illness*.
	Test results.	Test results.
	The fact that repressed anger can cause anxiety.	Not mentioned
Material originating from the patient thought to have been therapeutic.	Reporting suicidal fantasies.	Not mentioned.
	Recollection of wanting to hurl a book at a professor.	Not mentioned.
Transference factors thought to have been therapeutic.	Reassurance and support were effective because of his respect for therapist.	Reassurance and support were effective because of his respect for therapist.
	His fear of authority figures became less.	He was able to follow advice for the first time.
General picture of what happened.	As a result of achieving insight into his true feelings about his father and his father's death and of coming to grips with his hostile feelings toward his mother and authority figures in general this patient was relieved of severe anxiety symptoms. Reassurance regarding the nature of his illness was also a contributing factor.	By finding out that I am not in imminent danger of losing my mind and discovering that I have control over my impulses and a greater ability to assert myself than I had thought, I overcame my illness. The therapist offered direct advice and focussed the discussion to help bring about the resulting improvement.

the feelings of hostility which he had towards his mother, and came to realize that in many ways they were justified, and in all ways they were controllable, his anxiety was still further alleviated.

In his next-to-last interview, Bill discussed feelings of strong resentment which he had felt against some of his professors at school. He said that he had felt ashamed to tell me about them previously, and afraid that it would get him into some trouble with the school. He recalled one incident when a professor had asked him a question which he could not answer. At that moment he had wanted to hurl his textbook at the professor's head. He stated that he had not been sure at all that he would not be compelled to act upon the impulse, but that now he felt he would be in control of a similar impulse.

In his last interview, the eleventh in his treatment, which had extended over a period of five months, he said that his anxiety in lectures had entirely disappeared, and he also pointed out that he had developed a relationship with a new girl, which was replacing the one that he had had with Claire. He had not seen Claire for a period of over two months. She was planning to be married the following week and he was very glad about this.

Table 2 indicates the difference between the picture of what happened in therapy as sketched in by the patient himself, and by his therapist.

This project was designed only to demonstrate a research method. However, it is impossible to resist the temptation to formulate some tentative hypotheses.

There seem to be totally separate concepts of insight in the therapist's mind and in the patient's. The therapist thought of insight in terms of the unconscious factors which were made conscious, and thereby lost their threat, and also of the new awareness of the correlation of childhood experiences with present symptoms. The patients seemed totally to deny that this sort of thing occurred, and to regard meaningful insight only in terms of gaining a changed self-image or a changed perception of other people. Does this mean that the unconscious material brought to awareness, and the childhood memories recollected, were emphasized by the therapist in his summary because he was looking for them all the time, and convinced that they must be the significant factors, while actually they were completely unessential? Or does it mean that this unconscious material and memory came to awareness only briefly, their significance grasped only momentarily, and that they have now slipped out of reach so that the results alone remain in the patient's awareness?

The relationship between the therapist and the patient is outlined in the sections of the tables labeled transference factors—transference here being used in its more general sense indicating the total interaction between patient and doctor and not in the more limited orthodox psychoanalytic context. Here there is considerable agreement as to degree of helpfulness. Both patients agreed with the therapist that the reassurance given in the instance of the report of the tests for Bill and the special night visit for Paul was important in the eventual relief of symptoms. Both also felt that an encounter with a new kind of authority figure—one who was firm but still completely accepting—brought to each a new ability to deal not only with their own previously repressed feelings about authority but also greater ease in dealng with elders and superiors. The value of a warm doctor-patient relationship in establishing a climate conducive to getting well is not sufficiently stressed today when the emphasis in many quarters is still on the coldly objective impersonal qualities of the relationship which are felt by many to be essential to effective therapy.

The description of the turning points in therapy also reflects the lack of importance that the patient attributed to the uncon-

scious or to the recollection of childhood episodes. The emphasis of the therapist is on new knowledge or new awareness, that of the patient on events. For instance: finding a new girl friend, or, the therapist's coming out at night. Again, the patient seems to want to deny that there is anything mysterious about what happened; he wants to pin the result on simple, factual occurrences. Both patients had very definite ideas about what happened, and also about how it happened. The "what" had to do with the new knowledge about themselves, and a new concept of other people in their environment; the "how" seemed to be the chance to discuss themselves and these people with an impartial, intelligent, specially-trained, "safe" person. Apparently they felt that all they needed was to work things out for themselves from this vantage-point; the therapist's only function, as they look back upon it, was a sort of referee; he told them when they were wrong, fetched the ball when it went off the field and kept the game going. The therapist, on the other hand, saw himself as the one who helped the patient unlock his unconscious, and to utilize feelings and memories thus released to effect a change in his behavior. Which one of these explanations of what happens in therapy is accurate, or what combination of the two tells the true story, remains to be determined by further research. We feel that the method which we have described is one which will be useful in making this determination.

THE TREATMENT OF DRUG-RESISTIVE CHRONIC SCHIZOPHRENICS

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There is now no doubt that new drugs such as the phenothiazine derivatives are very important in the treatment and management of schizophrenia. Much enthusiasm has gone into the evaluation, regulation of dosage, and combined use of various "tranquilizers." In the midst of this enthusiasm, it is becoming increasingly apparent that despite all efforts there remains in all studies a group of apathetic, chronic schizophrenics who simply fail to show any appreciable response to medications. The authors were interested in devising a practical method of inducing improvement in such a patient group.

BACKGROUND

One of the authors was involved in a recent study (2) comparing the relative effects of reserpine, chlorpromazine, and a combination of these medications on a group of chronic schizophrenics. Despite many encouraging results, there remained a certain number of patients who failed to demonstrate more than a minimal degree of improvement. It was apparent from the first that the majority of these unresponsive patients could be distinguished from the rest of the group. Although the group as a whole tended to be quiet, apathetic, and withdrawn, these particular patients were remarkably so and generally would have been described as not only chronic, but deteriorated. All of the classic diagnostic categories of schizophrenia were represented in this drug-resistive group, although a majority would have been classified as "chronic undifferentiated." In the terminology of Kantor (11), these patients might have been better described as "process" schizophrenics whose chances of recovery are minimal.

After virtually all of the patients on the psychiatric continued-care service of the Salt Lake Veterans Administration Hospital had been treated extensively with medications, it was possible to collect one ward of "left-over" patients. Since the members of this group were generally so apathetic and indifferent to their environment, they presented few difficulties in management, but release from the hospital was impossible unless they could have received personal supervision to see that they even fed and dressed themselves adequately.

In devising a hypothesis to explain the evident lack of responsiveness in these patients, not only to medication, but also to their environment, the authors agreed on one concept. It was apparent that these individuals had accepted without protest an adjustment on a psychotic level. In the word "comfortable" was found the most universal adjective to describe the adjustment of these patients. The patients who had previously responded to medication, despite chronicity, had shown at least a token resistance to the psychotic process which affected them. The drug-resistive cases, however, had no conflict to escape. They had found a satisfactory means of adjustment and lacked any motivation to

[1] Veterans Administration Hospital, Salt Lake City, Utah. The authors appreciate the assistance of the Research and Development Division of Smith, Kline, and French Laboratories which supplied all drugs used in this study.

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get away from it. Generally they appeared content, adjusted, not anxious, and, in a word, comfortable.

Review of the literature indicates that this concept is a common one. Campbell (3) describes a group of deteriorated schizophrenics of this type as suffering from schizophrenic "surrender." Arieti (1) in his *Interpretation of Schizophrenia,* states that in advanced stages, "the patient seems to have accepted his illness." Later he also states, "... at this stage the patients seem to have no anxiety. As a matter of fact they seem contented. ... They seem to have achieved what they wanted; that is, they seem to have acquired self-esteem and to have removed anxiety." Of special significance have been several studies by Cowden and others (4, 5, 6, 7) who note that improvement with medications occurs in patients who maintain a high level of anxiety. In Cowden's recent (7), and excellent, article on the psychophysiology of schizophrenia, he has evolved a theory regarding these drug-resistive patients based on Selye's General Adaptation Syndrome (15). The patients selected for the present study correspond to Selye's stage of exhaustion. Cowden (7) correlates this by explaining, "They no longer manifest any anxiety because they are physiologically exhausted and anxiety is a physiological phenomenon." It is interesting that in the common expression, "burned-out schizophrenia," there must be much the same concept.

RESEARCH HYPOTHESIS

The hypothesis for this study has been more observational than analytic. Cowden's theory, based on Selye's work, could have been applied as an analytic theory offering at least a partial explanation for the lack of response of the drug-resistive patients, but offers little in terms of therapeutic approach. However, based on the observational hypothesis alone, a very simple research hypothesis was devised. It was believed that improvement from medications might result of it were possible in some way to create first, in this comfortable group of patients, some physiological "tension." It was more specifically hypothesized that apathetic, drug-resistive patients would respond to medication (particularly chlorpromazine) if they were first subjected to some method of inducing tension.

METHOD

Procedures for inducing tension. Several methods were considered in inducing "tension" in "regressed" psychiatric patients prior to, and in combination with, chlorpromazine administration. A chemical means of stimulating "tension" was finally chosen because it could be controlled and administered most easily. Ephedrine, dexedrine, and benzedrine were administered to a trial group of patients on another ward. Both palmar sweat measures (see following paragraph) and behavioral observations were collected to determine which of the three stimulating drugs was most effective. Ephedrine appeared to produce the most signs of "tension" as judged by increased palmar sweat and signs of hyperactivity, and was selected for and used in this study.

Measurement techniques. To establish accurately base lines and determine clinical changes in the selected patients, three methods were utilized. A recognized behavior scale and extensive psychological tests were applied for evaluation before, during, and following the study. A third simple, but effective, technique of measuring changes in physiological tension was used in both the pre-experimental and experimental phases of the study. This was the procedure of directly measuring changes in palmar sweating described at length by Mowrer (13). By this method, a chemically treated paper is placed directly on the index finger and held for a timed interval. A color change in the paper resulting from contact with perspiration varies directly in density with the amount of perspiration.

The production of palmar sweat is commonly accepted as a simple criterion of determining the general level, and changes in, physiological tension.

Selection of patients. Previous drug studies at this hospital (2, 12) left a residue of chronic schizophrenics who had failed to improve. All patients who had been tried for several months on reserpine, chlorpromazine, and a combination of these; who had shown little or no improvement as a result of these medications; who had received EST, and in many cases, IST, without lasting improvement; and who had a long-standing history of schizophrenia without known organic involvement, were considered for this study. Thirty-two male patients who best met the stringent criteria of non-improved, regressed schizophrenics, were selected and moved to a 32-bed ward. These patients ranged in age from 23 to 58 years and had been hospitalized for an average of eight to ten years. Of these patients, over 80 per cent were classified, by history, as "process" schizophrenics (11).

Drug Groups. Two patients were selected at random from the 32 and were given only placebo medications throughout the study. This was done primarily to have them available if, for any reason, any of the remaining patients had to be replaced. Fortunately, this did not become necessary and the two spare patients served as extra controls. To insure equitable distribution of the remaining 30 patients, they were first divided into groups of three by matching pre-drug palmar sweat levels. The patients in each group of three were then randomly assigned to form three groups of ten patients each.

All patients were removed from all medications three months prior to the beginning of the study. This three-month period allowed them to become accustomed to each other and to the ward. Two weeks before the study began, base-line data were collected for all patients (both behavioral adjustment ratings and psychological test data). With this design, each patient served as his own control.

Drug Group One (ten patients) received ephedrine for three weeks (200 mgm/day) and then received chlorpromazine-ephedrine combination (400:200 mgm/day) for twelve weeks.

Drug Group Three (ten patients) received ephedrine for fifteen weeks (200 mgm/day), and then chlorpromazine alone (400 mgm/day) for twelve weeks. By comparing Groups One and Three, it was possible to determine whether prolonged administration of ephedrine (fifteen weeks) is more effective than a short period (three weeks) of ephedrine medication prior to chlorpromazine. It must be noted that Group One received chlorpromazine and ephedrine in combination during the experimental phase, while Group Three received chlorpromazine alone during this phase. It was of interest to determine whether the two drugs in combination produced a more favorable result than ephedrine alone followed by chlorpromazine alone. This point was further clarified on a post-experimental phase with Groups One and Two.[2]

Drug Group Two (ten patients) was given chlorpromazine alone (400 mgm/day) throughout the pre-experimental phase (three weeks) and the experimental phase (twelve weeks). (It was fortunate that only one change was made in drug dosage for any patient in the study. This occurred when one patient developed too many unpleasant side effects and his medication was reduced to half of the designated dosage.) Group Two served as a modified control group to determine the effects of chlorpromazine alone, since all patients in the study had previously received this drug with little, if any, improvement. It was expected that the chlorpromazine group would show no significant behavioral improvement, which proved to be the case.

[2] See note at bottom of Figure 1 for explanation of pre-experimental, experimental, and post-experimental phases.

Group Three, during the fifteen-week pre-experimental phase, served as the control group for the effects of ephedrine since it was possible to determine whether or not fifteen weeks of ephedrine would result in any behavioral adjustment changes. The patients in this group showed no behavioral improvement during the fifteen-week period, as is shown in the section on Results.

Drug administration. All patients received oral medication in the morning, at noon, and at evening. Throughout the study, all patients received the same number and color of capsules and tablets. Even those patients receiving none or only one active medication were given placebos identical in color and size to the chlorpromazine tablet or ephedrine capsule. This insured that none of the personnel who were involved with the evaluation of the patients were aware of the identity of any patient in any drug group, nor were the patients aware of any differences in medication. This system satisfies the requirements of a double-blind experimental design.

BEHAVIORAL ADJUSTMENT DATA

The basis for measuring changes in behavioral adjustment for all patients throughout the study was the MACC Behavioral Adjustment Scale (10). This scale describes a patient's level of Motility, Affect, Cooperation, and Communication, along with a Total Adjustment Score. The MACC scale has been found to be valid in evaluating degrees of mental illness and in estimating readiness for discharge in psychiatric patients (9).

The base-line MACC Behavioral Adjustment scores were obtained for each patient just prior to the initiation of the study, at the end of the first three weeks (pre-experimental phase for Group One), and each four weeks thereafter. There were five raters for each patient: an aide, a ward nurse, and three activity therapists (occupational therapist, manual arts therapist, and corrective therapist). Each rated all the patients at the time of each rating. All five raters were well trained (test-retest reliabilities were found to range between .80 and .91) and dealt with all thirty-two patients daily.

The five scores from each rater at each rating period were averaged to obtain a "composite" score of the patient's typical, overall behavioral adjustment level. The actual amount of behavioral change was calculated for each patient and for each group for the three months of the experimental phase and the three months of the post-experimental phase (Groups One and Two).

Psychological test data. Psychological tests were given prior to the study and at a point coinciding with the end of the pre-experimental, experimental and post-experimental phases. All patients were given four standard psychological tests and a fifteen-item word-association test. The four psychological tests included a standard Memory for Objects Test, a Digit Span Test, a Digit Symbol Test, and a Speed of Tapping Test. Standard procedure was followed in the administration and scoring of these tests. Each patient was tested individually during a two-day period. During the base-line testing period there were 39 test refusals out of a possible 160 (five tests, 32 patients). The number of refusals dropped to fifteen out of a possible 160 at the end of the experimental phase (see section on Results).

RESULTS

Behavioral adjustment changes. From Figure 1 it appears that both groups treated with ephedrine prior to chlorpromazine showed significant behavioral improvement, while the group treated with chlorpromazine alone showed less behavioral improvement. Table 1 indicates that both Groups One and Three improved significantly during the three months of chlorpromazine medication, while Group Two (no ephedrine prior to chlorpromazine) did not. These re-

sults, then, would appear to confirm the original hypothesis. It is also significant that the group treated with chlorpromazine after fifteen weeks of ephedrine showed the largest behavioral improvement. The two patients held in reserve on placebo medications throughout the study showed no changes in behavior, palmar sweat levels, or in response to psychological testing.

The mean scores on Table 1 can be converted into percentile scores to enable the reader to see how much behavioral improvement really occurred. Group One had a base-line percentile score of 30 (33.4), and improved to the 42d percentile (36.2). Group Two moved from the 22d percentile (31.4) to the 30th percentile (33.6). Group Three moved from the 22d percentile (31.5) to the 42d percentile. Prior to the study, the patients as a group were at the 24th percentile as compared to the behavioral adjustment of psychiatric patients when measured by the MACC Scale. After twelve weeks of medication, Groups One and Three improved to the 42d percentile, which is still below that of the average psychiatric patient, even though they had improved significantly during the twelve weeks of medication.

Post-experimental phase. To make an additional assessment of the effect of the chlorpromazine and ephedrine given in combination (Group One) as compared to the administration of the drugs only in sequence (Group Three), Group One was taken off the combination and given chlorpromazine alone for twelve weeks following the experimental phase. In this post-experimental phase, they continued to improve at the same rate of change, and reached the 50th percentile (38.0). Group Two was given a combination of ephedrine and chlorpromazine following fifteen weeks of chlorpromazine alone during the experimental phase. This group, on the combination of drugs, actually declined slightly in behavioral adjustment.

Thus, for these data, it would appear that the ephedrine must *precede* the administration of chlorpromazine to obtain the best behavioral improvement with severely regressed schizophrenic patients. The

TABLE 1

Significance of Mean Behavioral Adjustment Changes for all Three Drug Groups

Drug Group*	Base-line Mean	Post-Experimental Phase Mean	Mean Score Gain	t ratio	Significance
Group 1	33.4	36.2	2.8	2.56	.05 level
Group 2	31.4	33.6	2.2	1.41	N. S.
Group 3	31.5	36.2	4.7	2.77	.05 level

* See note at bottom of Figure 1 for explanation of Drug Groups.

FIG. 1. Mean Behavioral Adjustment Changes for All Three Drug Groups*

Total Adjustment Centiles	Corresponding Adjustment Score	Base Line	Pre-Experimental Phase*	Experimental Phase		
				First 4 weeks	Second 4 weeks	Third 4 weeks
42%	36.5					
40%	36.0					36.2[1]
					35.5[1]	36.2[3]
38%	35.5					
36%	35.0				34.6[3]	
34%	34.5			34.5[1]		
32%	34.0					
30%	33.5	33.4[1]				33.6[3]
				33.1[3]		
28%	33.0		32.9[1]			
					32.6[2]	
26%	32.5		32.4[3]			
				32.0[2]		
24%	32.0					
22%	31.5	31.5[2]	31.5[2]			
		31.5[3]				
20%	31.0					

* *Group One* ([1]) received ephedrine alone for three weeks (pre-experimental phase) and then chlorpromazine-ephedrine for twelve weeks (experimental phase). *Group Two* ([2]) received chlorpromazine alone during the pre-experimental phase (three weeks) and the experimental phase. *Group Three* ([3]) received ephedrine alone for fifteen weeks (pre-experimental phase) and then chlorpromazine alone for twelve weeks (experimental phase). Thus, for Group One the pre-experimental phase lasted for three weeks. For Group Three, the pre-experimental phase lasted for fifteen weeks. As noted above, Group Two remained on chlorpromazine for the entire fifteen weeks.

combination of ephedrine and chlorpromazine resulted in little, if any improvement *unless* preceded by ephedrine alone. The best result was obtained with fifteen weeks of ephedrine alone, followed by twelve weeks of chlorpromazine.

Psychological test changes. In all test analyses, any patient who refused to cooperate in taking a test was not included in the analysis since a zero score would not have been a true measure of his ability on that particular test.

Statistically significant improvement (at the .05 level or better) was shown on Memory for Objects Test, Digit Symbol Test, and Digit Span Test, for Group Three at the end of the experimental phase. Group Two showed statistically significant improvement (.05 level or better) on Memory for Objects and shortened reaction time on the Word Association Test. Of the five tests given, only the Speed of Tapping Test resulted in no significant changes for any group tested. It would appear that Memory for Objects was most susceptible to the effects of chlorpromazine, whether the drug was administered alone (Group Two), following ephedrine (Group Three), or in combination with it (Group One). This conclusion is limited by the fact that there was no adequate control group. This study was primarily designed to control the effects of the drugs alone and in combination, rather than providing the type of control group adequate for psychological test interpretation.

Probably the most important finding, however, was that no group showed a *decrement* on test performance following chlorpromazine. Apparently the kinds of psychological test functions required in the performance of the five tests chosen were not negatively influenced by chlorpromazine. Such was not the result of a study reported by Porteus (14) in which he found a consistent decrement on his Maze Test following four months of chlorpromazine administration to "chronic" schizophrenics.

Out of 50 possible refusals for each drug group (ten patients, five tests), Group One had ten refusals during base-line testing, five at the end of the experimental phase; Group Two had seventeen refusals at first, eight at the end of the experimental phase; Group Three had twelve refusals, dropping to only one at the end of the experimental phase. The incidence of refusal change is consistent with the behavioral adjustment changes.

Thus all groups seemed to show a significant increase in performance and test scores on at least two, to a maximum of three, of the five psychological tests given following the experimental phase. Since there were significant changes on three of the five tests for Group Three, and one refusal only at the end of the experimental phase, this tends to support the results shown by behavioral changes.

DISCUSSION

The results of this study have indicated that the hypothesis was substantiated at a statistically significant level. Thus, if "tension" is induced in chronic, placid schizophrenics prior to the administration of chlorpromazine, significant (statistical) improvement can be expected in the majority of these patients.

Although significant clinical improvement—in terms of the indices described—was obtained, greater changes such as complete restoration of normal personality functioning did not occur for several reasons. First, the past history of the majority of the patients indicated a life-long marginal adjustment. Such patients could not reasonably be expected to reach a really adequate level of adjustment regardless of the treatment used. Second, the dosage schedule remained constant for all patients (except one) throughout the study. This constant-dosage schedule was deemed desirable in preference to adjusting dosage

levels for the maximum therapeutic effect for each individual patient, to allow a better comparison between drug groups. Third, the physiological method used may not have produced the desired level or type of tension which may best be produced by purely psychological means. Last, and probably most important, is that it was not felt that there was complete success in creating a really effective and lasting level of physiological tension. Analysis of weekly palmar sweat measures for all patients indicated that ephedrine produced an increase in palmar sweat for three weeks, with the measures increasing little beyond that point. If there had been more success in inducing a much higher and persistent level of physiological tension, dramatic improvement might have resulted. That statistically significant improvement did occur in the two experimental groups does suggest, however, that the method is based on a sound hypothesis.

SUMMARY AND CONCLUSIONS

1. A double-blind study was carried out to test the hypothesis that a drug-resistive group of chronic schizophrenics would respond to chlorpromazine if treated initally with a medication designed to induce physiological tension. A 32-bed experimental ward was set up, the patients consisting only of those who had previously failed to respond to extensive medication with chlorpromazine and other ataractic drugs. Following a pilot study, ephedrine was selected as the stimulating drug and was administered in doses of 100 mgm. both morning and noon. Two groups (ten patients each) who were given chlorpromazine (200 mgm. both at noon and evening) following a period of ephedrine medication, improved significantly in their behavioral adjustment; while one group (ten patients) given chlorpromazine alone did not improve significantly.

2. The timing factor was found to be extremely important. On the basis of this investigation it would apear that ephedrine must *precede* the administration of chlorpromazine if maximum effects are to be obtained. Neither the administration of ephedrine and chlorpromazine in combination, nor the addition of ephedrine following a period of chlorpromazine administration, resulted in any improvement beyond that which would have been anticipated from the chlorpromazine alone.

3. Psychological testing revealed that when significant changes did occur, they were always in the direction of improved performance. No decrement on psychological test performance was observed as a result of chlorpromazine administration.

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RECENT ADVANCES IN THE CHEMISTRY OF THE CEREBROSPINAL FLUID

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In recent years there has been a major revision of our concepts about the formation of cerebrospinal fluid. CSF is not only an ultrafiltrate formed by way of the choroid plexuses in the ventricles, but is also the product of an exchange between the blood and the central nervous system at all levels of the subarachnoid space. The isotopic work upon which this concept is founded has, in part, been summarized by Sweet and his co-workers (104). It may be deduced from this that the CSF is in a state of dynamic equilibrium, not just with the blood, but also with the interstitial fluid of all parts of the central nervous system. Thus the CSF is in a unique position to reflect such changes in the properties of neural tissue as may occur in disease. This serves to emphasize the important contributions made by the many recent chemical studies of the CSF. The application of modern laboratory techniques, such as electrophoresis, chromatography, spectroscopy, and flame photometry, to the investigation of the CSF has yielded a better understanding of neurologic diseases, as well as information of practical value in their diagnosis.

The purpose of this review is two-fold; first, to inform the reader in a comprehensive manner of the many recent investigations of the CSF, and second, to evaluate these in terms of their clinical importance. Some discussion of the chemical methodology is thought essential to these goals.

PROTEINS

There have been many investigations of the CSF proteins, beginning with ammonium sulfate fractionation studies by Kafka (52), and in recent years, employing electrophoretic and immunochemical techniques (30, 79). Most of this work was initiated in an attempt to understand the mechanism of the color changes in the colloidal gold sol reaction, especially as related to multiple sclerosis. Kafka early had shown that an excess of globulin in the CSF precipitated a colloidal suspension, while albumen exerted a protective action. This explanation was only partial, for fluids of identical albumen, globulin, and total protein content produced different colloidal gold reactions (52). More definite information awaited the application of physico-chemical methods to the separation of CSF proteins.

Kabat and his co-workers examined CSF from normals and patients with various neurologic diseases, using moving boundary electrophoresis (50). They found an increase in the gamma-globulin fraction in multiple sclerosis and in central nervous system syphilis, two diseases which account for the majority of abnormal gold tests. These results were confirmed by Schneider (98), Wallenius (112), Gries *et al.* (43), and others (89), all of whom employed paper electrophoresis. Press (86) confirmed earlier observations of Maclagan and Bunn (73). These workers had shown that the albumen, alpha, and beta-globulin fractions of CSF or serum inhibited coagulation of the gold sol, while the gamma globulin produced it (73). In addition, Press identified a protein of slow migration rate, for the most part contained in the gamma-globulin fraction of CSF but not serum. When this protein, obtained by ultra-centrifugation, was added to CSF specimens which previously gave positive gold tests, the coagulation failed to develop. Dilutions of serum consistently

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gave positive gold reactions, presumably because serum lacked the protective protein.

The investigations outlined above and numerous others disclosed some interesting characteristics of CSF proteins. Although, as Field indicated (26), they are for the most part identical with serum proteins, the various fractions occur in different proportions. There is more globulin in CSF than in serum, relative to the albumen content (79, 43). (A/G ration = 1 to 1.4). Much of the globulin is in the beta-fraction; the alpha-globulins are not well defined. There is also evidence for the presence of certain proteins in the CSF which have no counterparts in the serum. Fisk and his co-workers (27) described a rapidly migrating electrophoretic component of CSF designated "x" or pre-albumen which was not present in serum. Its mobility was 70 times that of albumen and it was found in every CSF specimen studied. Another even faster fraction x_1 has been identified (45). Uzman and Bering (107) believed that x and x_1 are complex mixtures of acidic large polypeptides.

An immuno-electrophoretic study by Gavrilesco *et al.* (34), suggests that these rapid components are not found exclusively in CSF. After electrophoretic separation (on agar), antibodies to serum proteins precipitated a pre-albumen fraction from serum as well as CSF.

Bucher *et al.* (17) demonstrated a material with a mobility between beta and gamma globulin in each of ten CSF samples. Hoch and Chanutin (45) also found this "t" component but not in all fluids. This may represent fibrinogen although, according to Kabat *et al.* (50), fibrinogen does not occur in CSF unless the total protein exceeds 100 mgs. per cent.

The gamma-globulins of the CSF are probably produced within the nervous system, at least in certain diseases (26). Elevations of gamma-globulin are more frequent and proportionately greater in the CSF than in the serum of multiple sclerosis patients (89). Antibodies to mumps virus (67) and Taenia (80) have been detected in CSF, as well as to reagen, and treponema (26). However, increased serum gamma-globulins in cirrhosis and multiple myeloma are often accompanied by an increase in CSF levels, despite absence of clinically evident involvement of the nervous system (74).

Electrophoretic separations of the CSF proteins require the concentration of large amounts of fluid. This is necessary because of the low total protein content of the CSF, which rarely exceeds 2 per cent, even in disease. Although many methods of concentrating CSF have been employed, they all are time-consuming, and introduce potential sources of error. For these reasons, paper electrophoresis is not suitable as a routine examination of the CSF. Since the elevated gamma-globulin in multiple sclerosis held promise as a diagnostic aid, several workers developed more practical methods to determine the CSF gamma-globulin.

Kabat and his co-workers (51) applied immunochemical techniques to the study of the CSF protein fractions. They found an elevated gamma-globulin in 85 of 100 cases of multiple sclerosis, as well as in neurosyphilis and a few examples of other diseases. Kabat *et al.* (117) later reported an extension of this investigation to 244 patients with multiple sclerosis. Of this total, 66.5 per cent had increased CSF gamma-globulin levels. The gamma-globulin was also elevated in 74 per cent of neurosyphilitics, but in only three per cent of patients with diseases other than multiple sclerosis or central nervous system syphilis.

Roboz, Hess and Forster (88), employing a zinc sulfate precipitation method based on a qualitative test proposed by Donovan and his co-workers (23), substantially confirmed the work of Kabat *et al.* Ziegler and Ross (118), also using the zinc sulfate method, found the gamma-globulin to be elevated in 73 per cent of patients with multiple sclerosis. Saifer and Narby (95), precipitating gamma-globulin with a lipid emulsion, presented data in close agreement

with the results of Kabat and his colleagues. Another method for the determination of CSF gamma-globulin by methanol precipitation has been proposed by Salt (97), but has not yet been extensively applied.

The gamma-globulin of the CSF rises proportionately as the total protein increases. However, when it exceeds 13 per cent of the total protein, this is considered especially significant for the diagnosis of multiple sclerosis or neurosyphilis (51). The gamma-globulin must always be considered in relation to the total protein. Elevations are of greatest diagnostic value when the total protein is normal. According to Kabat *et al.* (51, 117), there is no relation between the type of onset, course, or occurrence of new symptoms in multiple sclerosis and the increase in CSF gamma-globulin. Roboz (88) states that in some cases the rise and fall of the gamma-globulin mirrors the activity of the disease. The highest incidence of CSF gamma-globulin elevations appears to occur in cases of multiple sclerosis who have had many attacks, multiple lesions, and have marked functional disability (117).

Certain diseases beside multiple sclerosis and neurosyphilis are associated with an increased CSF gamma-globulin. The hypergamma-globulinemia of multiple myeloma and cirrhosis is reflected in the CSF (74, 79). The group of demyelinating diseases commonly referred to as the post-infectious encephalomyelitides (also post-vaccinal) may be associated with elevated CSF gamma-globulin (51, 117). Elevations have been reported in periarteritis nodosa and other "collagen diseases" (51, 117). Among neurologic conditions, adhesive arachnoiditis (36), and very rarely, neoplasms, may produce increases in the gamma-globulin. It must be remembered that a change in the CSF gamma-globulin probably represents an immunologic response on the part of the nervous system to any of a variety of antigens, and is not specific for any particular diseases.

The CSF gamma-globulin level is a more sensitive index of abnormality than the colloidal gold test, as it is usually performed. Freedman and Merritt (31), in a review of 2,629 cases of multiple sclerosis, found an abnormal colloidal reaction in 58 per cent, with a first zone curve in 24 per cent. The frequency of abnormal gold tests is partially dependent upon the sensitivity of the method employed, which in turn is determined by arbitrarily "adjusting" the conditions of the reaction. Unfortunately, when the sensitivity is increased sufficiently to yield abnormalities in most cases of multiple sclerosis and neurosyphilis, a larger proportion of miscellaneous conditions also give positive tests (102). On theoretical grounds the measurement of a constituent of the CSF such as the gamma-globulin, even though somewhat inaccurate, is preferable to an empyric test so dependent upon arbitrary conditions for its results. Practically, the gamma-globulin is a better diagnostic aid when the number of "false positives" is considered.

Each method for the determination of gamma-globulin appears to have a good clinical correlation. Although the lipid-protein flocculation method is considered simple by its originators, it necessitates dialysis of CSF and a number of steps (95). Because the immunochemical determination requires special skill in the preparation of anti-sera (31), the zinc sulfate precipitation technique is probably more suitable for use in a clinical laboratory. The amount of gamma-globulin precipitated by the zinc sulfate reagent is dependent on pH and ionic strength, and so close attention to these factors is necessary in performing this test (88). Whatever method is chosen to precipitate the gamma-globulin, it must then be determined by a protein analysis. For consistency the precipitated gamma-globulin and the total protein should be determined by the same method.

In addition to the gamma-globulin, other electrophoretic fractions may have diagnostic importance. Cumings (22) reported

an increase in the beta-globulin of the CSF in patients with malignant brain tumors. Fluid from cystic tumors also had considerable beta-globulin. Cumings' results were based on paper electrophoresis. The development and application of chemical or immunochemical determinations of beta-globulin to the study of the CSF might be useful in diagnosing brain tumors. Saifer and Zymaris (96) have studied the alpha-globulins of the CSF and serum by precipitation with a cationic detergent (Octab) at a pH of 6.65. The turbidity developed was then read in a nephelometer. Since much of the CSF lipoprotein migrates with the alpha-globulins, changes in the latter may have special significance in demyelinating diseases. Increases of alpha-globulins were found in syphilis, meningitis, poliomyelitis, and in multiple sclerosis (96).

A brief comment on the determination of the total protein in CSF is warranted because of its great clinical importance. No method currently employed is completely satisfactory, as is indicated by the frequent appearance of new modifications in the literature (85). Most commonly the biuret (113), tyrosine (29), or sulfosalicyclic acid (6) methods are used. Each of these has disadvantages. Each depends on a different characteristic of proteins, which is assumed to remain constant at widely different protein concentrations, and in health and disease. Despite theoretical objections to this assumption, any of these methods will give useful and reproducible results in the clinically important range if used with attention to detail. Wikoff and Kazdan (115) showed close agreement between the tyrosine and sulfosalicylic acid methods and the micro-Kjeldahl analysis. The normal range of the CSF total protein must be considered in relation to the age of the patient. Newborn infants have a high protein, presumably because of a poorly developed blood-brain barrier (68). The total protein also tends to be higher after the age of 60 (75), and tends to greater increases in disease than it does in younger individuals (78).

AMINO ACIDS

The identification and quantitative estimation of the free amino acids in CSF was made possible by the development of paper chromatographic techniques. Walker, Telles, and Pastore (111) identified aspartic, glutamic, and aminoacetic acids, as well as serine, threonine, glutamine, alanine, tyrosine, valine, phenylalanine, and leucine in many specimens. Less frequently found were gamma-aminobutyric and alpha-aminobutyric acids, histidine, lysine, asparagine, cystine, and arginine. Of all these compounds, glutamine was present in the highest concentrations. Glutamine was determined by measuring the ammonia liberated by acid hydrolysis, with a correction for ammonia derived from urea.

Whitehead and Whittaker (114) stated that leucine, valine, alanine, glycine, serine, and glutamine were the free amino acids normally present in CSF. The concentration of each of these was less than in the plasma with the exception of glutamine. These workers reported increased CSF glutamine levels in cases of cirrhosis of the liver, and in hepatic coma, with the highest values in the latter. Velasco and Ducci (109) confirmed these observations, and noted normal glutamine concentrations in the CSF of patients with cerebral hemorrhage, diabetic coma, and hypoglycemia. The elevated CSF glutamine in patients with severe liver disease may be produced as part of a detoxication mechanism which rids the CSF of the excess ammonia present in this disorder (72).

Ludewig (71) found traces of glutamic acid in CSF, and no gamma-aminobutyric acid. He reported there was no correlation between the CSF glutamine concentration and various neurologic diseases. Ludewig used microbiologic methods to determine glutamine and glutamic acid.

Logothetis (70) found an amino acid content of the CSF which was, with a few exceptions, similar to that reported by Walker *et al.* (111). He noted an increase of all free amino acids in cases of hereditary cerebellar ataxia, and a decrease in presenile psychoses. CSF tyrosine was diminished in patients with multiple sclerosis.

The chromatographic analysis of free amino acids is laborious, despite the application of semi-automatic devices (70). CSF must be concentrated, desalted, and deproteinized. These procedures result in some loss of amino acids. It is doubtful that chromatography of the CSF amino acids is suitable for application on a wide scale.

ENZYMES

Kaplan and his co-workers (54, 55) were among the first to study the enzymes of the CSF in health and disease. They determined trypsin, anti-trypsin, phosphatases, amylase, lipase, tributyrinase, and esterase. Phosphatases were the only enzymes consistently present in normal fluids. The others were present in meningitis and could be related to the polymorphonuclear cell count in the CSF. One case of multiple sclerosis had a high lipase activity. Colling and Rossiter (19), using phenyl phosphate as a substrate, determined the acid and alkaline phosphatase activity in the CSF of normal individuals and of patients with meningitis, poliomyelitis, and syphilis. While activity was found in less than half of the normals, it was present and considerable in the patients with meningitis and poliomyelitis. There was a good correlation between activity and the total protein and cell count. Kalsbeek and his co-workers (53) detected tributyrinase activity in some spinal fluids, and ascribed this to the action of lipase.

Several investigations of CSF cholinesterase have been conducted, motivated by the physiologic importance of this enzyme in neural transmission. Both true and pseudocholinesterases have been found in human CSF, but unlike the serum, the true or beta-methylcholine hydrolizing cholinesterase constitutes the major fraction (53, 87, 106). This may be a reflection of the content of the nervous system, which consists almost exclusively of the true enzyme (106). The CSF cholinesterase level is only 1/200th of the activity of serum (53), and appears to be independent of the serum level (106). Tower and McEachern (105), employing the Warburg method of gasometric analysis, found a decrease in the true cholinesterase of the CSF and an increase of the pseudocholinesterase in patients with head trauma. Colling and Rossiter (18) reported that the pseudo-cholinesterase of the CSF was increased in meningitis and poliomyelitis and paralleled increases in total protein, but not cell count. Jefferson (49) showed that protein levels over 100 mg per cent were associated with an increased pseudo-cholinesterase activity. Okinaka *et al.* (82) have noted elevated cholinesterase levels in malignant but not benign brain tumors. Bernsohn and his co-workers (14) found a high true cholinesterase activity in seven cases of myasthenia gravis, and an increased aliesterase (hydrolizing phenyl acetate) in cases of the Guillain-Barre syndrome.

There is agreement among several authors that there are no significant differences between multiple sclerosis and other diseases in respect to CSF cholinesterase activity (14, 49).

Kovacs (58) discovered that when CSF obtained from meningitis patients was incubated at 37°C there was a marked increase in inorganic phosphorus. This CSF liberated phosphorus and sugar when incubated with bovine brain and cord emulsion (59). He then studied the "neurolytic properties" of CSF more specifically by incubating CSF samples from patients with a variety of diseases with the appropriate substrates for the enzymes ribonuclease (60), desoxyribonuclease (62), and lecithinases (61). All these determinations were based on the

measurement of released inorganic phosphorus. The CSF ribonuclease was greatly increased in meningitis and poliomyelitis (60). Elevations were also found in convulsive disorders and some degenerative diseases (60). Similar changes in desoxyribonuclease activity were found, except in poliomyelitis (62). Lecithinases were increased in inflammatory diseases (61). Houck (47) has noted ribonuclease elevations in the CSF of patients with brain tumor, cerebral infarction, and multiple sclerosis. He used a new turbidimetric method (46).

The glutamic oxalacetic transaminase (GOT) activity in the CSF and serum of patients with neurologic diseases has been surveyed by a number of workers. We reported (Green *et al.* 37, 40) that the GOT level of the CSF was increased in 64 per cent of patients with cerebral infarction. Serum levels were normal. While the CSF GOT was elevated in a few cases of multiple sclerosis, it was normal in brain tumors. Patients with high serum GOT activity, and no evidence of central nervous system involvement, had normal CSF levels. Fleisher and his co-workers (28) reported results which differed from the above in several respects. They found the GOT of the CSF to be almost the same as that of the serum in their control group. We, and others (40, 56, 69), have variously estimated the CSF GOT level at ½ to ⅔ (approximately) of the serum activity in normal individuals. This figure is in good agreement with Wakim and Fleisher's own results in dogs (110), whose cerebral tissue resembles that of humans in respect to transamination (39).

Fleisher and his colleagues (28) reported elevated GOT activity in the CSF of patients with cerebral atrophy and convulsive disorders, results at variance with our data. These, and other investigators (56), did not find as high an incidence of GOT increases in the CSF of patients with cerebral infarction as we reported. Some workers also noted more frequent serum elevations (69). There was agreement on the existence of a blood-brain barrier for GOT and a lack of correlation between CSF activity and protein content (40, 69). In a later communication (41) dealing with 90 cases of cerebral infarction, we noted increased GOT in the CSF in 66 per cent. There were occasional elevations of serum GOT. Elevated CSF activity was found in a few cases of brain tumor, detracting from the value of the GOT determination in the differentiation of cerebrovascular disease from neoplasms (41).

Bruns, Jacob, and Weverinck (16) were evidently the first to report a normal CSF value for lactic acid dehydrogenase (LDH). Interest in this enzyme stemmed from the demonstration of elevated serum levels in neoplastic diseases (44). We have found (41) increased LDH activity in the CSF of all brain tumor patients studied (N = 16), with highest values in those with malignant tumors. Fleisher and his group (28) reported elevations in a few cases of astrocytoma. Wróblewski, Decker, and Wróblewski (116) found CSF LDH activity above the normal range in patients with intracranial neoplasms. Jakoby and Jakoby (48), on the other hand, reported elevated activities in cerebrosvascular accidents, but essentially normal CSF levels in patients with brain tumors. We also noted increased CSF LDH activity in patients with cerebrovascular disease, as well as in brain tumor patients (41). An independence of serum and CSF LDH activity was demonstrated (41, 116).

Anlyan and Starr (4) found an increased beta-glucuronidase activity in the CSF of patients with glioblastoma multiforme, but normal activity in those with benign tumors. These findings were not explained by the enzyme content of tumor homogenates. Similarly, we were not able to relate changes in the CSF GOT or LDH level to the concentrations of these enzymes in brain tumors (39).

A critical evaluation of the enzyme studies outlined above requires a consideration of the methodology employed in these various investigations. Regardless of which enzyme is determined, and the method employed, the results should be reproducible, if the necessary conditions described in the method are fulfilled. This is so when the activity of the enzyme bears a linear relation to its concentration, *e.g.*, a Zero order reaction obtains. Many of the reports on CSF enzymes do not define the type of the activity curve. This is particularly true of the studies on phosphatases (54), nucleases (60), tributyrinase (53), esterases (54, 106), and even of recent surveys of GOT and LDH (28, 56, 69). There is no proof presented that the activity measured is completely due to the enzyme purported to be determined. The commonly employed spectrophotometric determinations of GOT and LDH measure changes in optical density due to the oxidation of reduced diphosphopyridine nucleotide (DPNH). The validity of these methods is based on the assumption that under the conditions described, the oxidation of DPNH is attributable only to the specific enzyme reaction under study. We showed (40) that CSF frequently oxidized DPNH before any specific substrate was added. This was confirmed by Jakoby and Jakoby (48). Zero order activity may be obtained after a preliminary incubation of CSF and DPNH, to exhaust the endogenous activity. If LDH reactions are started with CSF instead of pyruvate a combination of endogenous activity and LDH is measured (41). The amount of endogenous activity in different CSF samples varies, and does not always parallel the GOT or LDH activity.

The method by which controls were selected in some studies may also be criticized. CSF was considered "normal" if the routine studies such as cell count, total protein, sugar, colloidal gold, and serology were within normal limits (54). Yet it has been shown that enzyme elevations may occur with no change in these other studies (40). Indeed, it is our impression that the LDH activity of CSF is a more sensitive index of disease than the total protein (39).

Several investigators have used CSF obtained from pneumoencephalographic studies, assuming that subarachnoid air injections do not influence the CSF enzyme levels. We have showed that marked elevations of GOT and LDH activity may be ascribed solely to this procedure (40, 41). Houck (47) has likewise found unpredictable changes in the CSF ribonuclease during air studies. Data is not available for other enzymes, but until it is, studies utilizing fluid removed during pneumoencephalography cannot be properly evaluated.

The source of CSF enzymes is not always clear. Kaplan (55) postulated three origins; from blood cells present in the CSF, from the blood due to an increased permeability of the blood-brain barrier, and from the tissues of the nervous system itself. To these we may add another source, the neoplastic cells of brain tumors. CSF pleocytosis may partially account for the elevated activities of trypsin (55), phosphatases (19, 55), pseudocholinesterase (18, 49), nucleases (60, 62), GOT (40), and LDH (41) reported in meningitis. A breakdown of the blood-brain barrier is probably also responsible, because in meningitis increased enzyme activity often is associated with an elevated total protein (19, 49). The origin of elevated enzyme levels in degenerative and neoplastic diseases of the central nervous system is not so easily explained.

Changes in the blood-brain barrier for enzymes which have a high ratio of serum to CSF activity may occur, but would hardly explain the occasional elevations of serum activity observed in these cases. We must note here that the demonstration of a "barrier" to the entrance of an enzyme into the CSF has usually been based on conditions during health, or in certain systemic illnesses (40, 69). Conclusions based upon such evidence do not necessarily apply to

the blood-CSF relationships in neurologic diseases. The lack of correlation between enzyme activities and the protein content of the CSF, in vascular and neoplastic diseases of the central nervous system, does argue against a hematogenous origin of the enzymes.

It seems probable that in many cases of cerebral infarction the increased CSF activity derives from the release of enzymes from the brain. Whether these enzymes originate from necrotic tissue is a matter of conjecture. Enzyme levels do not always parallel the amount of tissue destruction, as deduced clinically or observed at autopsy (28, 41). The problem is even more difficult in the case of brain tumors. Attempts to explain CSF activities by the enzyme content of the neoplasms have been unsuccessful (4, 39).

CARBOHYDRATES

The determination of the reducing substances in the CSF has long been a valuable aid in the differential diagnosis of meningitis. Eastham and Keay (24) showed by chromatographic techniques that, specifically, glucose and fructose were reduced in the CSF of patients with bacterial meningitis, while the hexosamine content was unaltered. The reason for the decrease in CSF sugar in bacterial meningitis is not fully understood. Baltch and Osborne (7) could not explain the lowered sugar levels they observed in dogs with experimental pseudomonas aeruginosa meningitis on the basis of bacterial and white cell glycolysis. A decrease in the CSF sugar is not specific for infectious diseases, since it has been reported to occur also in neoplastic involvement of the meninges (92).

Bauer (11), and Baudouin and his associates (10), studied the protein-bound carbohydrates of the CSF, using paper electrophoresis with staining by the Schiff reaction. Most of the glycoproteins migrated with the beta-globulin fraction, some with the alpha-globulin, and little with the gamma-goblulin and albumen. Stary and coworkers (100) determined the hexose content of the CSF protein precipitated by trichloracetic acid. According to Apostal *et al.* (5), the method used by Stary and his group did not include the seromucoid fraction of the glycoproteins. Roboz and her co-workers (90, 91) developed methods for the determination of the hexose and hexosamine content of the glycoproteins, mucoproteins, and alpha-glycoprotein in the CSF. Glycoproteins were precipitated by ethanol from CSF which had been lyophilized and extracted with acetone-ether. Hydrolysis of the precipitated glycoproteins was accomplished, using Permutit Q. Hexoses were then determined by chromatography. The carbohydrates bound to the gamma-globulin could be separately determined by precipitating this protein fraction with zinc sulfate. Roboz and her colleagues applied these methods to the study of the CSF in patients with different neurologic diseases (5). The total polysaccharide (bound to protein) content of the CSF was increased in multiple sclerosis, neurosyphilis, cerebral thrombosis, symptomatic epilepsy, infectious polyneuritis, and in brain tumors (5). The greatest increase was found in brain tumors. The ratio of the "gamma-polysaccharide" to the gamma-globulin in multiple sclerosis was significantly increased, possibly indicating antibody production (5).

Neuraminic acid, first isolated from the gangliosides of brain by Klenk (57), has been identified in both serum and CSF. This complex amino acid-sugar is found in the free form, and also bound to protein. Unlike serum, the CSF has a high proportion of dialyzable neuraminic acid, as well as a higher ratio of neuraminic acid bound to total protein (108). It has been shown that the neuraminic acid of the serum is bound principally to the alpha-globulin fraction (108).

The CSF neuraminic acid was reported increased in meningitis, cord tumor, and other diseases (93). It was decreased in schizophrenia (15).

It is difficult to interpret the increased polysaccharide content of the CSF reported in various neurologic disorders. Changes in the polysaccharides may reflect changes in the protein fractions to which they are bound. Since the polysaccharides are largely bound to the beta-globulin fraction, it is not surprising that both members of this complex are increased in the CSF of brain tumor patients (5, 22).

LIPIDS

There are few reports on the CSF lipids. The paucity of information is difficult to understand in view of the large amount of lipids present in nervous tissue. Kaplan (55), some time ago, urged the study of neutral fat, fatty acids, cholesterol, and cholesterol esters, in normal and abnormal CSF. It is likely that these investigations have been retarded by the lack of satisfactory chemical methods.

Baudouin, Lewin, and Hillion (9) found that CSF contained much less lipoprotein than plasma, and that which was present migrated with the alpha-globulin fraction. The serum lipoprotein, on the other hand, was contained predominantly in the beta-globulin. These workers used paper electrophoresis and stained with scarlet red. Bauer (11) confirmed these observations. Smith and his co-workers (99) investigated the CSF lipoprotein in patients with multiple sclerosis. They theorized that the breakdown of myelin which occurs in this disease might release substances into the CSF which could be identifiable as lipoprotein. Their results were not conclusive, although they found an abnormal lipoprotein corresponding to the albumen component on electrophoretograms.

Crosby and Weiland (21) observed that xanthochromia of the CSF was occasionally caused by the presence of lipid-like substances containing no iron or pyrrole groups. They thought that these chromogens might originate from destruction of central nervous system tissue.

Kumegai *et al.* (64) identified fatty acids of 4 carbon atoms in the CSF of patients with Japanese encephalitis, employing chromatography.

Cholesterol and cholesterol esters are present in normal CSF. Increased concentrations of these steroids have been found in neurologic diseases (83).

PIGMENTS

Oxyhemoglobin, methemoglobin, and bilirubin are the pigments which commonly occur in CSF (8). Oxyhemoglobin can usually be identified spectroscopically in the lumbar CSF within 2 hours after a cerebral hemorrhage. Bilirubin is present from the third or fourth day until the second or third week. Although methemoglobin is present in encapsulated subdural and intracerebral hemorrhages, it does not usually appear in the lumbar CSF. The xanthochromia of CSF which occurs with spinal subarachnoid block is probably due to bilirubin (8).

Bilirubin may be present in the CSF of jaundiced patients. Amatuzio, Weber, and Nesbitt (3) noted the direct reacting form in the CSF of most of the patients with cirrhosis or hepatic coma they studied. An increased total protein was associated with this finding. There was no correlation between serum and CSF bilirubin levels. Barrows and his colleagues (8) stated that in jaundiced patients the serum bilirubin level and the duration of the jaundice are important in the production of pigmented CSF. Our observations are more in agreement with Amatuzio *et al.* (38). We were unable to correlate serum and CSF bilirubin contents. Stempfel and Zetterstrom (101), investigating hemolytic disease of the newborn, reported that bilirubin present in the CSF during the first four days of life was

indirect reacting, and was associated with a high total protein.

ELECTROLYTES

When the CSF potassium ion concentration is altered experimentally, serious physiologic disturbances result (12). It is not surprising that this concentration is maintained within narrow limits. Bekaert and Demeester (12), and Cooper and his coworkers (20), have shown that in a variety of experimental and clinical conditions which markedly raised or lowered the serum K^+ there was no change in the CSF K^+. Radioactive K42 enters the CSF rapidly after intravenous injection until the CSF/blood ratio is 15–20 per cent, after which entry slows appreciably (13). There is normally a significant difference between the serum and CSF K^+ values, the former being higher (means; serum K^+ 4.45, CSF K^+ 2.96) (20). Radioactive sodium (Na) enters the CSF from the blood more slowly, but at a more constant rate than potassium (42, 104). There is no significant difference between the serum and CSF Na^+ concentrations, the CSF Na^+ tending to change with alterations in the serum level (20).

The calcium and magnesium ion concentrations of the CSF differ from those of the serum in that the CSF contains more Mg^{++} and less Ca^{++} (33, 103). The Ca/Mg ratio in CSF is 1.01 (103). There is little variation from this figure in normal specimens.

Mond (77) found no differences between controls and patients with various neurologic diseases in respect to the concentrations of potassium, sodium, and calcium, in the CSF.

The order of permeability of the halides into the CSF, reported by several workers (1, 42, 84) is chloride > bromide > iodide. The Cl^- concentration in the CSF is normally higher than in the serum, presumably because of a Donnan effect due to the low protein of CSF. Despite this concentration gradient, radioactive Cl^- 38 injected intravenously exchanges rapidly with the CSF (104). The CSF Cl^- determination is still of value in the diagnosis of tuberculous meningitis according to Gierson and Marx (35), who reported that the Cl^- concentration was persistently normal in only 7 per cent of 231 cases.

Br^- enters the CSF more slowly than Cl^-, and reaches much lower concentrations. This ion later re-enters the blood against a concentration gradient (84). Alpers and Rall (1) found the CSF iodide to average 1.35 per cent of the serum content. They also detected thyroxin in the CSF.

The inorganic phosphorus of the CSF is increased in many bacterial and viral meningitides (32). Kovacs' work (58) indicated that this phosphorus may be liberated from phosphorus containing constituents of the nervous system, such as nucleoproteins and phospholipids. Odessky and his colleagues (81) found a rough correlation of the phosphorus content and the CSF cell count, while Friedman and Levinson (32) reported the majority of phosphorus elevations were associated with an increased CSF protein. The serum phosphorus remained normal in these cases.

Lehmann and Kral (63, 66) have studied the iron content of the CSF in different psychotic conditions. The CSF iron is normally one tenth to one twentieth of the serum concentration (66). Of interest is the finding of increased CSF iron levels in patients with Parkinsonism (63), since the basal ganglia have been reported to have a high iron content (63).

Certain general deductions can be drawn concerning the CSF electrolytes. Ions such as K, Ca, and Mg which are known to profoundly influence neuronal conductivity, are closely regulated in their CSF concentrations. In the case of K^+, the CSF level has been shown to be uninfluenced by serum changes. The concentrations of all three ions, relative to each other, are different in the CSF than in the serum. This may have some special implications in regard to neuronal function.

Much of the work with radioactive isotopes indicates that there may be active mechanisms involved in the transport of electrolytes into and out of the CSF. Such mechanisms would seem to be essential to protect the central nervous system against potentially dangerous concentrations of physiologically active ions (42, 104).

OTHER CONSTITUENTS

Lasch (65) reported marked elevations of the CSF pyruvate concentration in patients with cerebrovascular accidents and brain tumors. This is of interest in regard to the DPNH oxidizing capacity of the CSF in these types of cases, observed by ourselves (40, 41), and Jakoby and Jakoby (48). These latter workers hypothesized that an abundance of pyruvate in the CSF would promote the reaction catalyzed by lactic dehydrogenase (upon the addition of DPNH), and thus explain the "endogenous" DPNH oxidizing activity of CSF. Lasch found that elevated serum pyruvate levels were always associated with increased CSF values, but that the reverse was not true, *i.e.*, neurologic diseases which elevated the CSF pyruvate did not always effect the serum level. Amatuzio and Nesbitt (2) reported the CSF of patients in hepatic coma contained an increased amount of pyruvate.

Martensson and Thunberg (76) studied the citric acid content of the CSF. The lumbar CSF contained more citric acid than the serum. Elevations of citric acid were noted in cerebrovascular accidents and brain tumors, but were greatest in the former group.

Acetylcholine has been found in the CSF of patients with head trauma (94, 105), and was identified in the CSF of 77 per cent of epileptics by Tower and McEachern (105). Whether the neurohumor plays an active role in the production of symptoms in these cases is uncertain. The hormonal substance serotonin, which is now being extensively studied in connection with psychiatric disorders has been found in the CSF of some patients with head trauma and brain tumors (94), but not in cases of multiple sclerosis (25). Biologic methods were used to determine serotonin. More information is necessary before the diagnostic and therapeutic implications of these studies can be appreciated.

CONCLUSION

While the brevity of several sections of this review may be attributed, in part, to the failings of the author, the conclusion is inescapable that many more investigations of the CSF are needed. The close cooperation of the clinical neurologist with the research biochemist should assure the accumulation of new data. However, progress is dependent also upon the supply of CSF furnished by all physicians who have the occasion to perform a lumbar puncture. The total amount of fluid removed is invariably in excess of that needed for routine tests. Rather than discarding the surplus CSF, the clinician is urged to send it to a research laboratory. He will thus further the acquisition of information which will ultimately benefit him in the diagnosis and management of patients with neurologic diseases.

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BRIEF COMMUNICATION

BASIC STUDIES IN MONGOLISM II. HEMOGLOBIN[1]

M. J. CARVER, PH.D.[2]

INTRODUCTION

Previous investigations indicate that mongolism may be primarily a result of a physiological injury during intrauterine stages of existence (1). The possibility exists that this insult to the fetus might result in a "biochemical lesion" reflected in the hemoglobin molecule much as anoxia is reflected in an abnormally increased rate of hemoglobin synthesis.

Differences in hemoglobin pigments are thought to be related to variance in the folding and coiling and in the amino-acid content of the polypeptide chain which constitutes the globin moiety. The present study was undertaken on the premise that a basic biochemical defect in mongolism may be one in protein synthesis which may in turn be mirrored in the presence of abnormal hemoglobin.

The methods of filter paper electrophoresis, column chromatography and alkali denaturation were applied to the problem of analyzing the blood of mongoloids for the type of existing hemoglobins. On the basis of electrophoresis at pH 8.6 the presence of a hemoglobin other than the principal component cannot be ruled out, whereas the column chromatography method (pH 6) and the alkali denaturation method, together, would indicate any type of hemoglobin whose concentration exceeds one per cent.

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MATERIAL AND METHODS

Hemoglobin solutions were prepared from blood samples of nine mongoloid patients ranging in age from 5 to 61 as follows: Blood obtained by venipuncture was oxalated and centrifuged at 2500 rpm for 10 minutes. The plasma was discarded and the cells were washed twice with physiological saline. One volume of cells was then shaken for 5 minutes with 1.8 volumes of distilled water and 0.4 volumes of toluene and the mixture centrifuged at 3000 rpm for 20 minutes. The clear red hemoglobin solution which forms between the toluene layer and sediment was drawn off and filtered before use. Twenty-five microliters of this solution was applied to the paper prior to electrophoresis which was carried out on the "sandwich type" plate glass apparatus using Whatman No. 1 paper sheets. Experimental conditions were as follows: Veronal buffer pH 8.6, ionic strength 0.1, current 20 mamp. for 16 hours at 4°C. Ion exchange column chromatography by the cuvette method of Huisman and Prins (2) and chemical analysis by the alkali denaturation procedure of Singer, *et al.* (3) were applied as supplementary means of studying each of the blood samples.

RESULTS AND DISCUSSION

Figure 1 indicates that the hemoglobin present in the red blood cells of mongoloids is normal adult hemoglobin. Extending the time of electrophoresis from 16 hours to 20 hours brought about no further separation. Column chromatography substantiated the results of paper electrophoresis showing only Hemoglobin A. Figure 2 is a typical chromatogram obtained in the

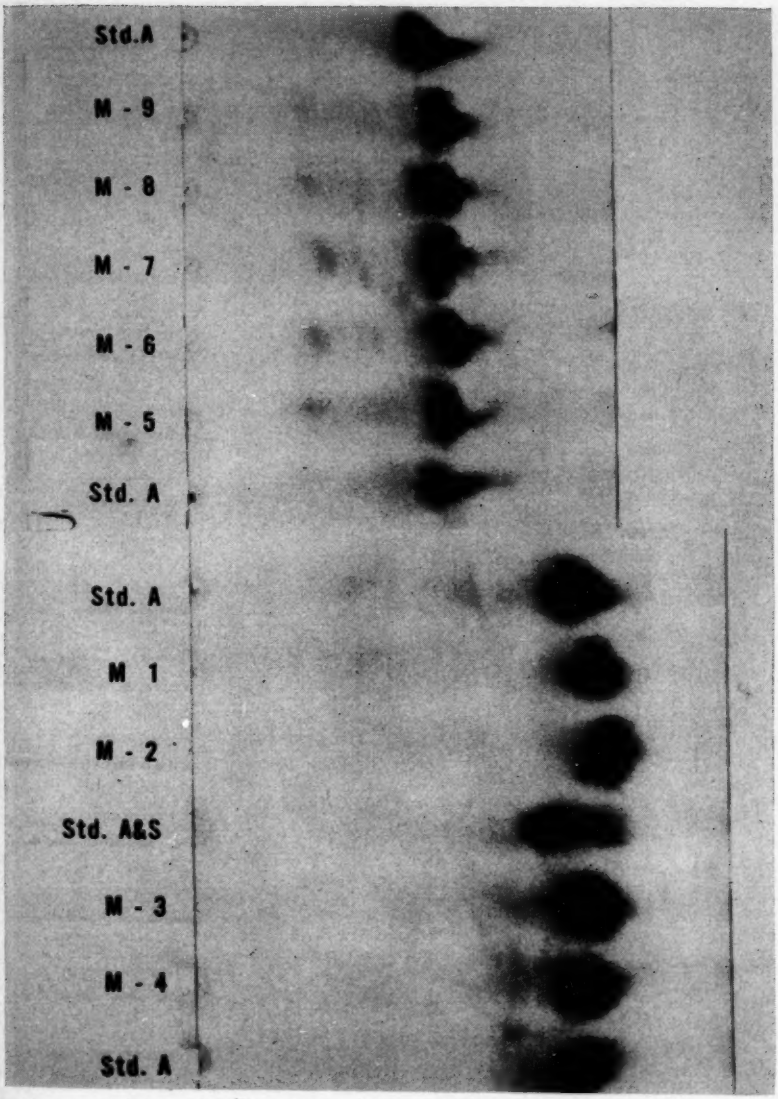

FIG. 1. (A) Electrophoretic patterns of hemoglobins in mongolism. Samples 5 through 9 with Hemoglobin A for comparison. Duration of run: 16 hours. (B) Electrophoretic patterns of hemoglobins in mongolism. Samples 1 through 4 with Hemoglobin A and Hemoglobin A and S mixture for comparison. Duration of run: 20 hours.

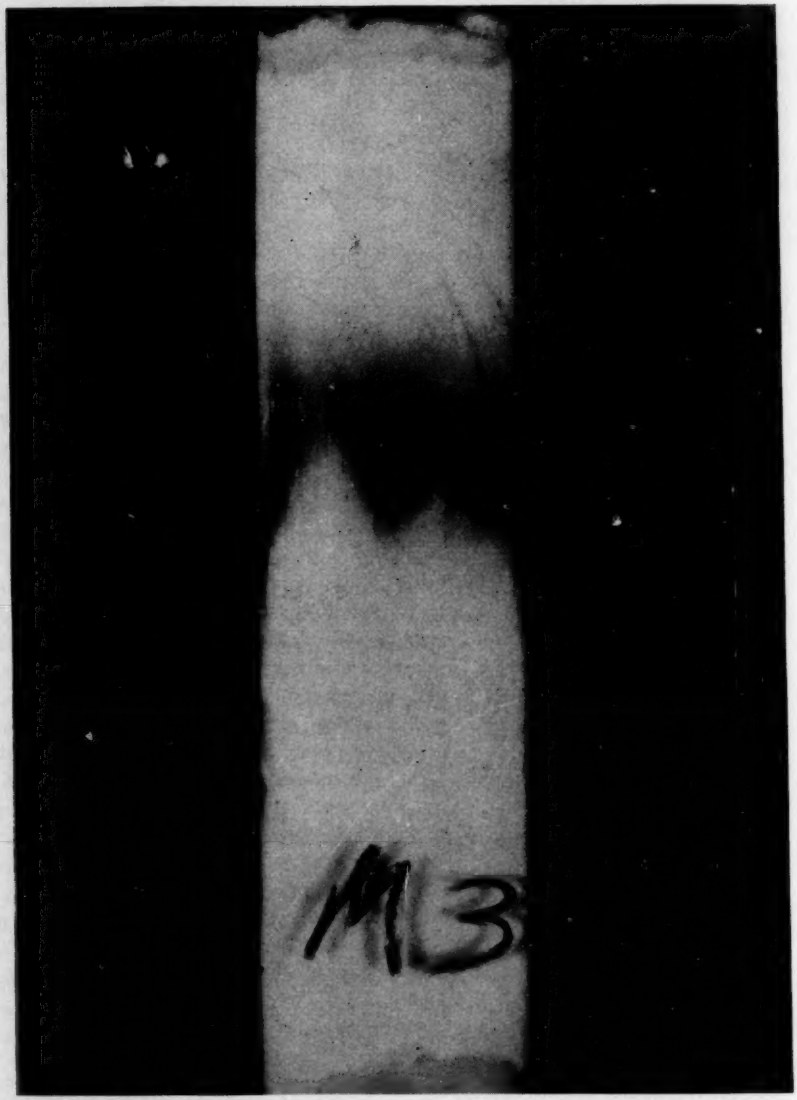

FIG. 2. A typical column chromatogram of hemoglobin in mongolism, showing a homogeneous substance, Hemoglobin A.

present study showing a homogeneous compound that migrates at the same rate as Hemoglobin A. Alkali denaturation studies indicated that each of the blood samples contained less than one per cent fetal hemoglobin. These data would indicate that if errors in protein formation are characteristic of mongolism, these are not portrayed in the hemoglobin molecule or if these errors are reflected in the hemoglobin pigment they, at least, cannot be resolved by the present-day techniques.

SUMMARY

Investigation of hemoglobins prepared from the blood of mongoloids revealed Hemoglobin A as the principal component. Other hemoglobins, if present, do not exceed a concentration of one per cent.

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BRIEF COMMUNICATION

CLINICAL EXPERIENCES WITH -2-PHENOTHIAZINE SULFONAMIDE DIMETHANESULFONATE IN CHRONIC PSYCHOTIC PATIENTS

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A clinical trial of the drug, N,N-dimethyl-10-[3-(1-methyl-4-piperazinyl)-propyl]-2-phenothiazine sulfonamide dimethanesulfonate (Figure 1), was prompted by pharmacological studies indicating activity in animals similar to that of chlorpromazine and prochlorperazine. In addition to certain fundamental similarities, this compound was found to have an antiemetic action 49 times more potent than chlorpromazine and was found to be three times more potent in blocking the conditioned escape response in rats (1).

Freedman and Giarman (2) have advanced the hypothesis that the tranquilizing efficacy of a phenothiazine drug may be predicted from its anti-emetic action. According to these authors the chemoreceptor trigger zone, which is located in the area postrema and upon which apomorphine acts in producing emesis, is adjacent and functionally bound to those areas of the reticular formation which control various autonomic, postural, and extrapyramidal activities. If such a functional relationship can be assumed to exist, -2-phenothiazine sulfonamide dimethanesulfonate should possess very considerable tranquilizing activity.

The drug was tried on 19 adult male chronic schizophrenic patients whose ages ranged from 27 to 53 years and who had been hospitalized for a number of years. Included in this sample were seven paranoid patients who had been on phenothiazine treatment immediately prior to the study and four hebephrenics, three catatonics, three undifferentiated types, and two mental defectives who had received no such treatment. Those patients who were already receiving phenothiazine medication were discontinued after an initial evaluation. All patients were then placed on oral placebo medication for four weeks, and then changed over to the drug. The dosage schedule was 0.8 mg. daily for one week; 2.0 mg. daily for the second week; 4.0 mg. daily for the third week, and 8.0 mg. daily from the fourth to the twelfth week, at which time treatment was stopped. The efficacy of the drug was determined by weekly evaluations of the patients by the authors working independently of each other. Periodic laboratory studies of the blood and urine were also carried out.

During the three month drug trial period, little or no change was observed in the clinical courses of the 19 patients comprising the observed group. All maintained essentially the same status, although five of the patients appeared to develop an accentuation of their original apathetic states. The following complications were noted: five patients developed Parkinsonian reactions of varied degrees of severity; two patients developed hypotensive reactions; and seven patients developed elevated sedimentation rates for which no clinical basis could be found.

Clinical experiences with the drug -2-phenothiazine sulfonamide dimethanesulfo-

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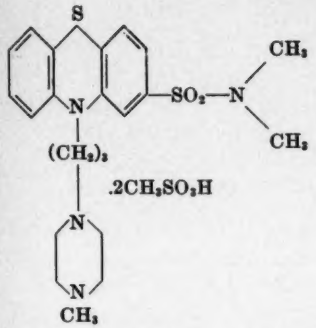

FIG. 1. Structure of -2-phenothiazine sulfonamide dimethanesulfonate.

nate in the treatment of 19 chronic psychotic patients utilizing 8.0 mg. as a daily dosage for the last eight weeks of a twelve week treatment period, indicated that the drug yielded little or no therapeutic effect over and above that produced by previous phenothiazine and/or milieu treatment. These results would seem to indicate that increased potency in terms of anti-emetic activity and conditional avoidance response as indicated by animal experimentation, does not necessarily bring about an increased tranquilizing effect, illustrated by the fact that the patients in this present study did not reach a clinical level of improvement beyond that reached previously.

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